DE CONSTITUTIE VAN CANTHARIDINE

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PROEFSCHRIFT

TER VERKRIJGING VAN DEN GRAAD VAN DOCTOR IN DE FACULTEIT DER WIS- EN NATUURKUNDE AAN DE RIJKS-UNIVERSITEIT TE LEIDEN, OP GEZAG VAN DEN RECTOR-MAGNIFICUS Dr. L. VAN ITALLIE, HOOGLEERAAR IN DE FACULTEIT DER WIS- EN NATUURKUNDE, VOOR DE FACULTEIT TE VERDEDIGEN OP DINSDAG 8 MEI 1923, DES NAMIDDAGS TE 3 UUR

DOOR

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GEBOREN TE NOTTINGHAM, ENGELAND

A. W. SIJTHOFF'S UITGEVERSMAATSCHAPPIJ — LEIDEN
MCMXXIII

AAN MIJNE OUDERS

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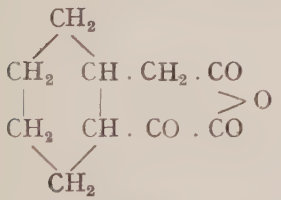
THE CONSTITUTION OF CANTHARIDIN.

I. *Introduction.*

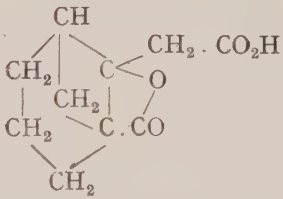
Cantharidin is a colourless, neutral substance crystallising in trimetric tables, melting at 218° and corresponds to the formula $C_{10}H_{12}O_4$. It may occur to the extent of as much as two per cent. in Spanish flies (*Lytta vesicatoria*), from which source it was obtained in quantity by ROBIQUET and THIERRY [1]), as long ago as 1835 and, although the literature on this substance is very extensive, its constitution is not yet definitely settled.

The earlier investigations of PICCARD, [2]) ANDERLINI, [3]) SPIEGEL, [4]) HOMOLKA, [5]) and their collaborators, although extremely important, cannot possibly be gone into in this communication. This earlier work has been very ably reviewed, however, by GADAMER [6]).

The first formula for cantharidin was suggested by SPIEGEL (I) but it was subsequently rejected in favour of (II) suggested by H. MEYER [7]).



(I).



(II).

In 1913 GADAMER [8]) published a preliminary communication, the first

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[1]) Ann. **15,** 315 (1835).
[2]) Ber. **12,** 577 (1879); **10,** 1504 (1877); **11,** 2120 (1878); **19,** 1404 (1886).
[3]) Gazz. chim. ital. **21,** (1), 457 (1891); **21,** (2), 56 (1891); **23,** (1), 121 (1893). Ber. **23,** 485 (1890); **24,** 1993 (1891).
[4]) Ibid. **25,** 1468, (2956 (1892); **26,** 140 (1893).
[5]) Ibid. **19,** 1082 (1886).
[6]) Arch. Pharm. **252,** 609 (1914).
[7]) Monatsh. **18,** 393 (1897); **19,** 707 (1898).
[8]) Verhand. Ges. deutsch. Naturf. u. Aerzte (2), 494 (1913).

of a very extensive series, in which he suggested still another formula (III), which will be considered later on.

In a second communication [1]), GADAMER made a complete review of the previous work on cantharidin and with new experimental data concluded as follows. The constitution assigned to cantharidin by MEYER necessitates the following conditions:

(*a*) Cantharidin must easily give cantharic acid; this is correct since MEYER obtained a 70 per cent. yield.

(*b*) Cantharic acid is given a γ-lactone structure and is a stable monobasic acid and should be more stable than cantharidin, which is represented as a β-lactone. Such β-lactones, however, easily lose carbon dioxide, whilst the β-lactones obtained by BAEYER and VILLIGER [2]) neutralise exactly two equivalents of hot alkali and do not reform the lactone on acidification. Contrary to this, cantharidin neutralises one and a half equivalents and on acidifying the solution it is again precipitated.

(*c*) Cantharic acid must be saturated and it must give the characteristic reactions of the secondary alcohol group. MEYER concluded that cantharic acid must be saturated, since it is obtained by the action of a reducing agent on a saturated compound, cantharidin, and bromine has no action on it. The reduction of alkaline permanganate observed by MEYER, was attributed to the secondary alcohol grouping in the lactone ring. BAMBERGER and LODTER [3]) however, proved that the acid in question was like a partially hydrogenated aromatic compound and reacted with bromine. Thus the balance of evidence clearly pointed to the fact that cantharic acid was unsaturated.

(*d*) The constitution of *iso*cantharidin follows easily from that of cantharic acid.

Against the explanation of MEYER, GADAMER points out that *iso*-cantharidic acid on boiling with water gives no trace of an anhydride, whilst on his hypothesis, cantharic acid on long boiling with an excess of alkali and acidifying should give *iso*cantharidinic acid but it does not.

(*e*) It is also pointed out in GADAMER'S criticism that the formula for cantharidin proposed by MEYER contains no less than three asymmetric carbon atoms and is nevertheless inactive, which is rather unusual in a natural compound but of course not impossible.

After disposing of the then accepted formula for cantharidin GADAMER brings forward his own views.

One of his collaborators, DANCKWORTT [4]), found that cantharidin dissolved in acetone neutralised more N/2 caustic potash than is required for one carboxyl group and he prepared also a dibasic brucine salt, which could not be resolved into isomeric forms. There-

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[1]) Arch. Pharm. **252,** 609 (1914).
[2]) Ber. **30,** 1954 (1897).
[3]) Ber. **21,** 838 (1888).
[4]) Arch. Pharm. **252,** 632 (1914).

fore cantharidin is the anhydride of a dibasic acid (cantharidic) and the state of combination of three of the four atoms of oxygen in cantharidin is definitely fixed. Continuing his investigations in a third memoir, GADAMER [1]) gives an account of the action of hydrobromic acid on cantharidin; in this way he obtained hydrobromocantharic acid and cantharidin dibromide, $C_{10}H_{12}Br_2O_3$, analogous to the diiodide of PICCARD. Therefore he concluded that the fourth atom of oxygen was present in an ether group; the action of halogen acids being,

$$R.O.R' + HI \longrightarrow R.OH \quad R'I + HI \longrightarrow RI \quad R'I + H_2O.$$

In the same paper an account is given of his studies of the action of hydriodic acid.

Hydrobromic acid acts very similarly to hydriodic acid. The product obtained with the former, (14 per cent), at 150°—155°, consisted of cantharic acid, the dibromide (m.p. 133°—134°), which can be distilled in a vacuum and like the diiodide of PICCARD acts as if it were an anhydride, *dl*-hydrobromocantharic acid (m.p. 218°—220°) and a mixture of other acids. The *dl*-hydrobromocantharic acid was resolved by means of its brucine salt. The dibromide is the final product of the action of hydrobromic acid on cantharidin, since it is unchanged by further treatment, while the hydrobromo-acid gives cantharidin, cantharic acid and dibromide. When however, the optically active hydrobromocantharic acids are treated in this manner, the products are found to be *inactive* cantharidin and cantharic acid of opposite sign to the hydrobromo-acid used. It was also observed that on heating *l*-hydrobromocantharic acid at 215°—225° in an atmosphere of hydrogen, the acid is quantitatively decomposed into hydrogen bromide, *d*-cantharic acid and *inactive* cantharidin, in molecular proportions. DANCKWORTT also demonstrated that the production of cantharic acid by MEYER'S method most probably depends on the intermediate formation of a hydro-halogen cantharic acid, while at the same time he points out that phthalide ω-carboxylic acid contains a similar grouping to that present in cantharidin, as suggested by MEYER, but these substances behave so differently towards dilute alkalis that they cannot be similarly constituted. DANCKWORTT also succeeded in resolving cantharic acid into its optically active components.

With regard to the constitution of cantharidin GADAMER concluded as follows. Cantharidin is optically inactive and active hydrobromocantharic and cantharic acids always give inactive cantharidin, hence the latter contains no asymmetric carbon atoms. Other work proves that the molecule contains a *cyclo*hexane ring with *ortho*-side chains and a *cis*-anhydride grouping and, since the molecule is incapable of resolution into optical isomers, it must be symmetrical.

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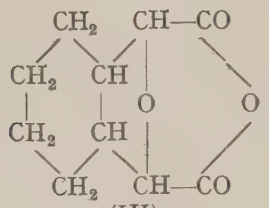
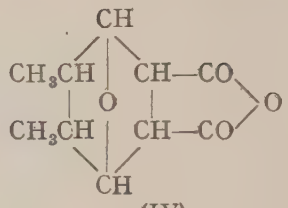
[1]) loc. cit. p. 636.

The only formulae consistant with these requirements and suggested by GADAMER are the following.


(III).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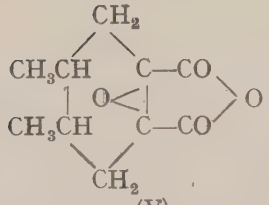
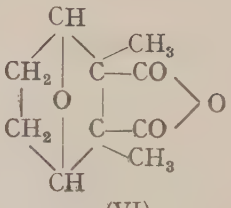
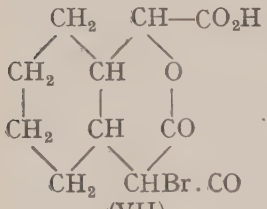

(V).


(VI).

Formula (V) however, and similar ones derived from (III) and (VI), were immediately rejected on the grounds of the instability of the ethylene oxide ring and formula (VI) met with a similar fate since it did not explain the production of a xylic acid, although neither does formula (III) for that matter. It was also supposed that it would not give cantharene readily, which was taken to be 1 : 2-dimethyl- $\triangle^{2:6}$-*cyclo*hexadiene. This formula however was revived after subsequent investigations. Therefore cantharidin was supposed to be either (III) or (IV); hydrobromocantharic acid (VII) or (VIII); cantharidin dibromide (IX) or (X) and cantharic acid (XI) or (XII).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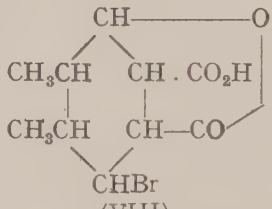
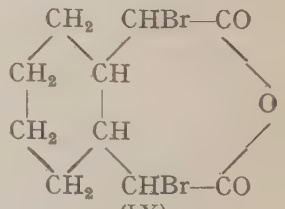

(VIII).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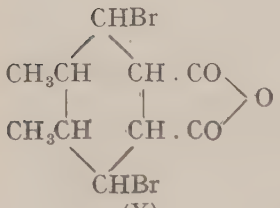
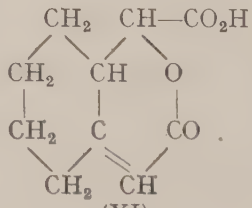
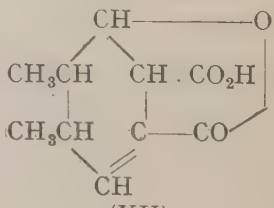

(X).


(XI).


(XII).

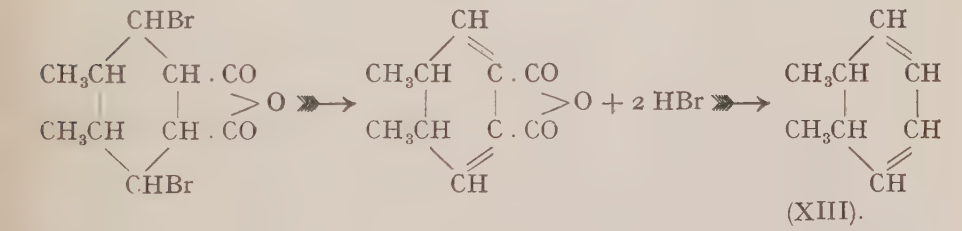
It will be noticed that the elimination of hydrobromic acid from hydrobromocantharic acid to form cantharidin and cantharic acid is

exactly similar to ether and olefine formation from a hydroxy alkylhalide. The elimination of hydrobromic acid, however, from formula (VIII) may take place in two ways giving two isomeric cantharic acids.

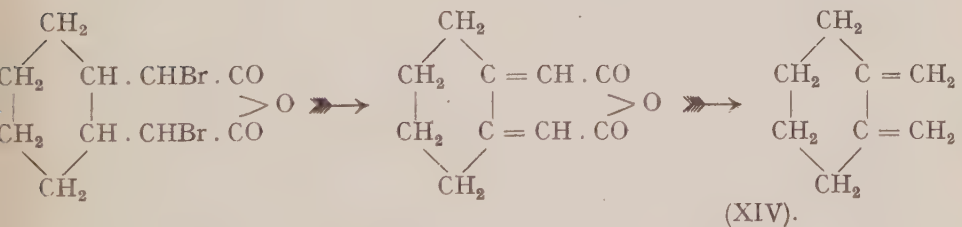
GADAMER gave preference to the acid represented by (XII) because he considered that the presence of a lactone ring would probably make the adjacent hydrogen atom more mobile but, as pointed out in the original paper, steric influences make this choice a rather doubtful one. Since only one cantharic acid is known, GADAMER considered it was evidence strongly in favour of formula, (III) for cantharidin, where isomerism is impossible.

The next portion of GADAMER'S communication deals with the probable constitution of *iso*cantharidin but since it proved subsequently to be non-isomeric with cantharidin itself, it is unnecessary to deal with his considerations, which were based on an erroneous empirical formula.

With regard to the production of cantharene from the dibromide, by the action of caustic potash, a parallel was suggested to the similar formation of cineol. [1]) The reaction was supposed to take place in two stages, hydrogen bromide being eliminated before carbon dioxide as follows:



(XIII).



(XIV).

Thus the hydrocarbon would appear to be either (XIII) or (XIV). Unfortunately the constitution of cantharene is not yet proved. HAWORTH'S [2]) synthetic-product was at this time considered to be identical with cantharene and was given the formula (XV), but AUWERS [3]) considers it is best represented by (XVI).

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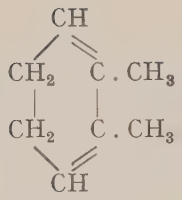
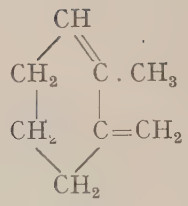
[1]) Loc. cit. p. 630.
[2]) J. Chem. Soc. **103**, 1245 (1913).
[3]) Ber. **46**, 2994 (1913).



(XV).



(XVI).

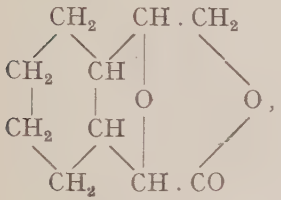
Should natural and HAWORTH'S synthetic cantharene prove to be identical, GADAMER states that formulae (XIII) and (IV), for cantharene and cantharidin respectively, become untenable. He therefore resuscitated formula (VI), which he had summarily rejected on the grounds that its dibromide would not give cantharene. He points out that if this formula be accepted, the production of cantharene, having the structure suggested by HAWORTH or AUWERS could be easily explained provided that the anhydride grouping is removed before hydrogen bromide. This assumption however, appears to be contrary to experience since the methyl ester of the dibromide when treated with potash, gives cantharene easier than the dibromide itself. GADAMER also suggests that the production of *o*-xylene by heating cantharidin with phosphorus pentasulphide, is best explained on formula (IV) and the production of paraxylic acid is only possible on this formula, unless profound isomeric changes take place during the process.

Thus the immediate outcome of the earliest memoirs of GADAMER and his collaborators was to prove that the constitution of cantharidin is probably represented by one of the formulae (III), (IV) or (VI), the preference being given perhaps to (IV). Subsequent investigations from the same laboratory endeavoured to settle which of these formulae is correct.

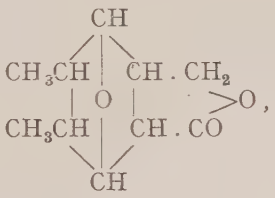
It is perhaps advantageous to summarise briefly the arguments against each of the above mentioned formulae. The chief argument against (III) was that it failed to explain why the supposed *iso*-cantharidin of ANDERLINI should be an anhydride and not a lactone. This objection, however, was completely set as nought when it was proved that *iso*cantharidin was not, what it was supposed to be. On the other hand this formula and also (VI), allow a ready explanation of the production of cantharene, assuming that it has the constitution assigned to it by HAWORTH or AUWERS, but (IV) would not give this particular compound if it is assumed that the hydrogen atoms on the α-carbon atoms to the carbonyl groups are removed as hydrogen bromide, in preference to those adjacent to the methyl groups. This would-probably be the case if hydrobromic acid is eliminated before carbon dioxide, since it is well known that the hydrogen atoms in the α-position to a carboxyl group are more reactive than those further removed. All three formulae explain the production of *o*-xylene, but only (IV) explains the occurrence of a xylylic acid in

the pyrogenic decomposition products of barium cantharate and should this acid prove to be 2 : 3-dimethyl-benzoic acid as was suggested by MEYER, then none of the above formulae can explain it satisfactorily.

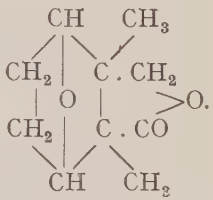
According to RUDOLF, [1]) cantharidin may be reduced in two ways, either the anhydride or the ether grouping being reduced. He points out however, that the former is the more probable since, as WISLICENUS [2]) proved, phthalic anhydride is readily reduced by zinc and acetic acid giving 30 per cent. phthalide, 30 per cent. phthalic acid and 20—25 per cent. diphthalyl. RUDOLF found that cantharidide the product obtained by reducing cantharidin with sodium and alcohol, has a molecular weight approximating to 182 ; it is not therefore, analogous to diphthalyl. It is a very stable lactone which could not be resolved into optically active isomers by means of its brucine salt. Its formula will be one of the following :



(XVII).



(XVIII).



(XIX).

It will be noticed here, that the last two are γ-lactones while (XVII) has a more complex system, containing an oxide and a lactone in one ring. It might be argued therefore, that the lactone ring in (XVII) would be less stable than that in the other formulae. Such an argument however, cannot be considered conclusive since compounds containing similar groupings, e.g. diethylene oxide and glycolide, are quite stable. By the action of zinc and dilute acids on cantharidin dibromide, RUDOLF also obtained a fairly good yield of deoxycantharidinic acid, $C_{10}H_{16}O_4$; melting at 160°—165° in a THIELE's apparatus. Deoxycantharidinic acid has rather peculiar properties. The analyses showed that RUDOLF was apparently unable to obtain it quite free from the corresponding anhydride deoxycantharidin. On fusion or on boiling with water, it is converted into the internal anhydride, which is volatile in steam ; thus if a solution of deoxycantharidic acid is distilled in steam, it is converted for the most part, into deoxycantharidin which may be extracted from the distillate. The silver and barium salts crystallise with one molecule of water and RUDOLF considers that the acid has properties very similar to tetramethylsuccinic acid. Deoxycantharidin is a rather unstable anhydride in spite of its easy method of preparation ; it is easily transformed into the original acid again in cold water, or by simply standing in air.

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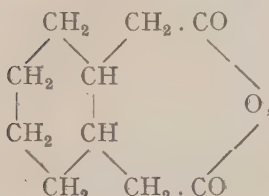
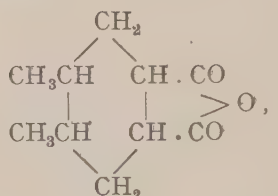
[1]) Arch. Pharm. **254,** 423—456 (1916).
[2]) Ber. **17,** 2178 (1884).

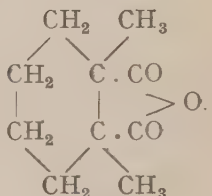
In deoxycantharidin, the two bromine atoms in cantharidin dibromide have obviously been replaced by two atoms of hydrogen; the compound is in fact cantharidin with the ether grouping reduced. The constitution of deoxycantharidin will therefore be represented by one of the following formulae.



(XX).



(XXI).



(XXII).

The first of these formulae, it will be noticed, contains a seven atom anhydride ring and on the grounds that such a structure could not exist, RUDOLF rejected the corresponding formula for cantharidin. The remaining two formulae however, are the anhydrides of hydrogenated phthalic acids containing five atom anhydride rings, and it would therefore appear highly probable, that such compounds would be very stable. On the other hand deoxycantharidin is quite unstable, which might be interpreted as evidence for formula (I), especially, when it is remembered, that numerous phenheptamethylene compounds are known to be quite stable and it has recently been proved by MOHR, [1]) that it is possible to arrange a three dimensional space model for such compounds, which is free from all strain. At any rate it cannot be claimed, that the evidence so far available with regard to deoxycantharidin, is sufficiently convincing to justify the complete rejection of this particular formula.

RUDOLF also showed that cantharidin dibromide on treatment with methyl alcohol and hydrobromic acid for one week, gave the acid monoester (m.p. 122° b.p. 132°—133°/14 m.m.), identical with GADAMER'S supposed dimethyl ester [2]), which appears incapable of existance. The difficulty experienced in esterifying the second carboxyl group was attributed by RUDOLF to steric hinderance and therefore, on this account, he considers that formula (VI) is more probably correct for cantharidin than (IV), in spite of the objections raised by GADAMER, since the close proximity of the two methyl groups to the carboxyl groups, may exert some such steric effect.

RUDOLF also prepared cantharene in a purer state probably, than previous investigators, by the action of caustic potash solution on cantharidin dibromide. In the meantime another synthetic cantharene had been obtained by MEERWEIN, [3]) by heating 1 : 2 dimethyl-$\triangle^1$-*cyclo*hexene dibromide, with quinoline. The physical constants of the cantharene prepared by RUDOLF, and the synthetic products of HAWORTH and MEERWEIN, are collected together in the following table.

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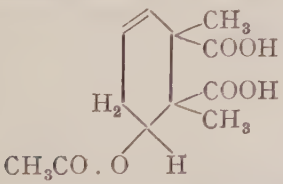
[1]) J. prakt. Chem. **103,** (2) 316 (1921).
[2]) Arch. Pharm. **252,** 631 (1914).
[3]) Ann. **405,** 148 (1914).

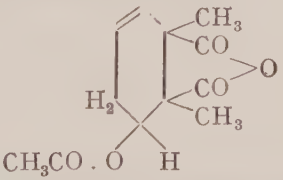
	HAWORTH	MEERWEIN	RUDOLF
Boiling point	135.5°	134°—137°	138°—139°
Density (d_4^{20})	0.8521	0.8373	0.8531 *
Refractive index (n_D^{20})	1.4895	1.46928	1.484801 *[1]
Molecular refraction	36.62	35.99	36.27

(calc. for C_8H_{12} = 36.01) (*These values are for $d_4^{18.6}$ and $n_D^{18.6}$)

A comparison of the above data, shows that no two agree throughout. Thus the products of HAWORTH and RUDOLF, agree fairly well as regards density and refractive index, but differ in boiling point by three degrees. Hence it is very doubtful whether these two products are the same substance or not. On the other hand the data of MEERWEIN would seem to show, that this product was different from either of the others since none of its properties are identical. He points out however, that his product probably contained a little 1 : 2 dimethyl-$\triangle^1$-*cyclo*hexene. A comparison of the three suggested formulae for this compound shows that in all probability the compound (XVI) would possess the largest optical exhaltation, and for this reason AUWERS considers that this represents HAWORTH's product. It is also probable that (XIII), having a simple conjugated system would have a higher exhaltation than (XV). PICCARD and MEERWEIN both succeeded in obtaining *o*-toluic acid by the oxidation of their cantharenes but RUDOLF failed. Therefore as regards the constitution of this important derivative his work leads us no further.

The year following RUDOLF's work GADAMER published three more memoirs. In the first [2]) he points out that RUDOLF's formula does not explain the formation of α-hemimellithylic acid in the pyrogenic decomposition of barium cantharate and the properties of ANDERLINI's *iso*cantharidin and *iso*cantharidic acid. On repeating the work of ANDERLINI it was found that a 120 per cent. yield of the so called isocantharidinic acid was obtained ; the latter on further investigation proved to be acetylhydrato cantharic acid, isocantharidin being the corresponding anhydride. These were formulated as follows :





thus GADAMER accepted RUDOLF's formula. Contrary to DANCKWORTT's statement it was proved that isocantharidin gave pure cantharic acid on hydrolysis.

In the second communication [3]) he deals with the reduction products

[1]) HARRIES and ANTONI, Ibid. **328,** 115 (1903), gave $n_D^{20} = 1.49118$, but their cantharene was polymerised to some extent.

[2]) Arch. Pharm. **255,** 277 (1917).

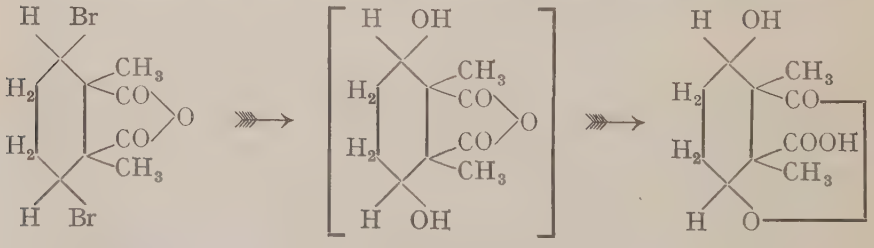
[3]) loc. cit. 290.

of cantharic acid. It is pointed out that of the three formulae suggested for cantharidin, (VI), the one accepted by RUDOLF should give only one dihydro cantharic acid while the others should give two isomeric acids. When reduced by PAAL and SKITA's method *l*-cantharic acid gave only one *l*-dihydrocantharic acid, *r*-cantharic acid gave only one *r*-dihydrocantharic acid whilst *l*-hydrobromocantharic acid with zinc and sulphuric acid gave *l*-dihydrocantharic acid and other products. These facts are considered by GADAMER to favour RUDOLF's formula but it should be remembered that several cases are known where reduction with platinum or palladium gives only one product where two are theoretically possible. More energetic reduction of cantharic acid with palladium and hydrogen lead to the production of dihydrocantharic acid and deoxycantharidin.

The third memoir [1]) was an attempt to clear up the discrepency regarding 2 : 3 dimethyl benzoic acid. From the products of the decomposition he isolated (a), a distillate consisting of water and cantharene, (b), a residue which on acidification and distillation in steam gave volatile acids, (c), and nonvolatile acids (d). From their odour the volatile acids were suggested to be angelic, α-methylbutyric and *iso*butyric acids but none were definitely isolated.

The remaining acids were separated into readily and sparingly soluble fractions and from the latter α-hemimellithylic and paraxylic acids were isolated in the ratio of 10 : 1. From these results GADAMER concludes that we have no alternative but to assume a migration of radicles during the pyrogenic decomposition.

The ninth communication on cantharidin from the Marburg laboratory appeared in 1920[2].) In this paper GADAMER describes the isolation of another acid from the product of the action of hydrobromic acid on cantharidin. It contains one carboxyl group and a lactone ring and readily gives a sulphuric ester, which on resolution with brucine is completely resolved into the leavo-rotatory isomer. The latter on hydrolysis gives the original cantharolic acid in its optically inactive form. This fact is explained by the unsymmetrical cantharolic acid giving a symmetrical hydrate, shown in brackets. Its production from cantharidin dibromide is explained as follows.



Quite recently two more memoirs have appeared [3]).

[1]) Arch. Pharm. **255,** 315, (1917).
[2]) ibid. **258,** 171 (1920).
[3]) ibid. **260,** 172, 199 (1922).

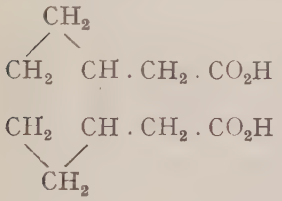
The first deals with an attempt to try and follow the action of chlorosulphonic acid on cantharidin in order to confirm DANCKWORTT's explanation of the formation of cantharic acid. This however was unsuccessful. Incidentally, *iso*cantharolic acid was obtained which is apparently a *trans*-cantharolic acid.

The second paper deals with the preparation of cantharidide by the reduction of cantharidin with hydrogen and nickel and the probable constitutions of the many known nitrogen derivatives of cantharidin.

A perusal of the evidence on the constitution of cantharidin so far available makes it certain that one of the three formulae suggested by GADAMER must be correct but there appears to be insufficient grounds for definitely accepting any one particular constitution. Also, considering the exhaustive work of GADAMER and his collaborators there would appear to be but little hope of deciding which of these formulae is correct from a further study of cantharidin itself. It was therefore decided to try and prepare some of the derivatives of cantharidin synthetically. *Of the many derivatives known, the simplest and one of the most characteristic, is without doubt deoxycantharidin and this substance therefore is the one chosen for this investigation.*

EXPERIMENTAL.

The experiments described below were made to obtain *cis-cyclo*hexane 1 : 2 diacetic acid and its anhydride in quantity, since if GADAMER'S first formula for cantharidin is correct, these substances should be identical with deoxycantharidic acid and deoxycantharidin respectively. LEROUX [1]) has already obtained a small quantity of an acid for which he proposes the above formula, by converting dekahydro-β-naphthol into octahydronaphthalene and oxidising the latter by means of chromic acid but the yield was very poor; only the analysis and melting point are given. His method was extremely laborious and unsuitable for the production of this acid in quantity, since β-naphthol, the starting material is hydrogenated only with great difficulty. At the end of his paper he states, that attempts to synthesise this acid by the reduction of *o*-phenylene diacetic acid with sodium amalgam and water and by the interaction of ethyl sodiomalonate and 1 : 2 dibromo*cyclo*hexane failed.

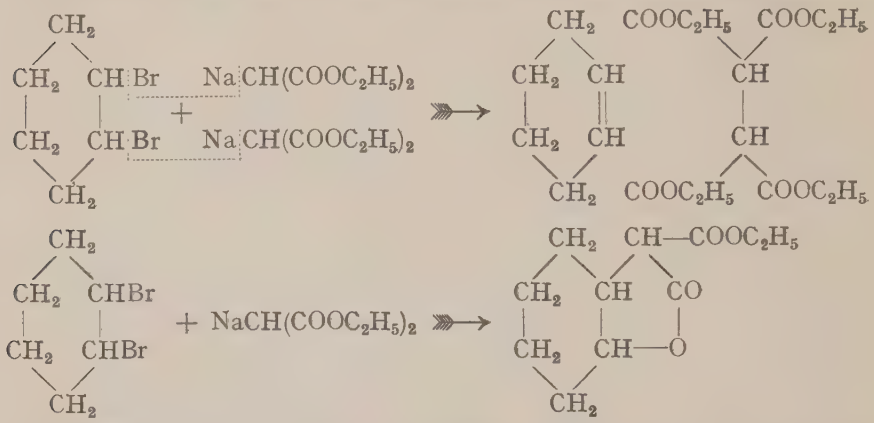


(a) *The interaction of ethyl sodiomalonate and* 1 : 2 *dibromo*cyclo*hexane.*

Preliminary experiments proved that dibromo*cyclo*hexene reacted with ethylsodiomalonate and this reaction has been studied in detail. In

[1]) Ann. chim. phys. (8) **21**, 458 (1910).

no case however has *cyclo*hexane 1 : 2 diacetic acid been obtained. The reaction takes two courses represented by the following equations:



The dibromo compound used in this investigation was prepared by adding the requisite amount of bromine in ice cold carbon tetrachloride to tetrahydrobenzene, which had been prepared according to BRUNEL'S method [1]), and carefully fractionating the product in a vacuum. The product thus obtained was a perfectly colourless liquid which could be kept indefinitely without darkening. Apparently no physical constants of this substance, with the exception of the boiling point [2]), are to be found in the literature; the following constants were therefore determined:

Boiling point 97°—98°/10 mms., 124°—125°/36 mms.; melting point -6.0 D_{16}^{16} 1.7917, D_{4}^{16} 1.7898; n_{D}^{16} 1.5540, M_D = 43.28 (calc.) 43.23.

Attempts were made to convert dibromo*cyclo*hexane into the corresponding diol or dicarboxylic acid with the idea of discovering whether it had a *cis* or a *trans* configuration, but without success. It is unchanged by heating with dilute alkalis at 150° or with water and silver oxide at 100°. Alcoholic potassium cyanide has no action on it, while with sodium acetate and glacial acetic acid at 180°, hydrogen bromide is eliminated giving a good yield of dihydrobenzene, which showed the characteristic colour reaction of the $\triangle^{1:3}$ compound, with concentrated nitric acid [3]).

Many experiments were carried out with dibromo*cyclo*hexane and ethyl sodiomalonate but only three representative experiments will be briefly described below. In this connection it is interesting to note that monobromo*cyclo*hexane reacts in the normal manner with ethyl sodiomalonate giving a 30 per cent. yield of *cyclo*hexylmalonic ester [4]).

[1]) Bull. soc. chim. **33,** 270 (1905).

[2]) See BAEYER, Ann. **278,** 108 (1894); MARKOWNIKOFF, ibid. **302,** 29 (1898); FORTEY, J. Chem. Soc. **73,** 984 (1898); CROSSLEY, ibid. **85,** 1415 (1904); HARRIES, Ber. **45,** 813 (1912).

[3]) CROSSLEY loc. cit.

[4]) HOPE and PERKIN, J. Chem. Soc. **95,** 1363 (1909).

The reaction was first carried out under the usual conditions. Ethyl malonate (50 grams) was added to a solution of sodium ethoxide, prepared from 7.2 grams of sodium and 150 ccs. of absolute alcohol, and dibromo*cyclo*hexane (37 grams) and the mixture boiled for 24—30 hours. Some sodium bromide separated but the liquid was still strongly alkaline. The reaction product was poured into water, the heavy oil extracted with ether, the extract dried over calcium chloride and after the ether had been removed, the residue, a brown oil, was distilled in a vacuum. The distillate was collected in three fractions, namely, a mobile fraction boiling at 65°—150°/24 mms., a viscous fraction boiling at 170°—180°/20 mms. and a solid fraction which distilled at 180°—190°/20 mms. The tarry residue amounted to 5 grams. On refractionation the following fractions were obtained.

(a) 70°—150°/20 mms. = 25 grams, (b) 150°—160°/20 mms. = 1.5 grams, (c) 160°—170°/20 mms. = 5.5 grams, (d) 170°—186°/20 mms. = 2.0 grams, (e) 185°—190°/20 mms. = 8.0 grams melting at 65°—67°.

The last fraction completely solidified on cooling and was readily soluble in most of the common organic solvents with the exception of light petroleum (b. p. 30°—40°). It crystallised very readily from alcohol or petroleum, in clusters of brilliant needles or rods. A further quantity was obtained by freezing fractions (b), (c), and (d) in light petroleum.

This substance was definitely proved to be ethyl ethane tetracarboxylate as follows. The melting point was 74.5°—75° and was unchanged when mixed with an authentic specimen of the ester. On hydrolysis it gave ethane tetracarboxylic acid from which a specimen of succinic acid was isolated; a quantitative experiment gave the following result:

0.5382 gram of substance neutralised 6.86 ccs. N . KOH hence equivalent is 81.8, $[CH . (CO_2C_2H_5)_2]_2$ requires 80.

On analysis;

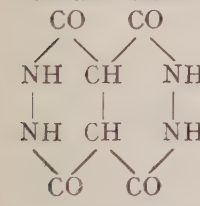
0.2106 gram gave 0.4044 gram CO_2, 0.1320 gram H_2O.

$C_{14}H_{22}O_8$, requires C = 52.82, H = 6.95 per cent.

found C = 52.37, H = 6.96 per cent..

The action of hydrazine on ethyl ethane tetracarboxylate.

In 1895 Saloman and Pohl [1]), claimed to have obtained a dihydrazide of ethane tetracarboxylic acid by the action of hydrazine on the ester. They described their product as having pronounced acidic properties; it was soluble in sodium carbonate solution and was reprecipitated by mineral acids, whilst with ammonia it gave a brown solid. They assigned to it the annexed formula but no practical or analytical details were furnished. Such a formula does not account for the strong acidic properties mentioned above; it was considered desirable therefore,



[1]) Ber. **28**, 1722 (1895).

to confirm these authors' statements. The following experiments show however, that even when the ester is boiled with an alcoholic solution containing an insufficient quantity of hydrazine, the normal tetrahydrazide of ethane tetracarboxylic acid is produced.

The ester (3 grams), and 1.5 grams of hydrazine hydrate, (90 per cent.), were dissolved in 150 ccs. of absolute alcohol and the solution boiled for three hours during which time, 0.7 grams of an insoluble solid separated. This was filtered off and the solution boiled for a further period of two hours and allowed to cool over night, when a further 0.3 gram was obtained. On further heating with fresh hydrazine hydrate for two hours 0.5 gram was obtained making 1.85 grams in all. From the mother liquors 0.5 gram of ester was recovered.

The *tetrahydrazide of ethane tetracarboxylic acid* is a colourless crystalline solid, which melts with decomposition at 210° after darkening at 205°. The melting point however, varies slightly with the rate of heating; the value given above was obtained with a rate of approximately one degree per second. It is very sparingly soluble in all organic solvents. It dissolves in hot water giving a strongly alkaline solution, due no doubt to hydrolysis, but cannot be recrystallised from this solvent. It is also soluble in cold sodium carbonate solution but is not reprecipitated by acids and it gives no colouration with ammonia. On analysis:

0.1510 gram gave 52.2 ccs. of N at 14° and 769.8 mms., N = 41.0 per cent.
$C_6H_{14}O_4N_8$, requires N = 42.7 per cent.

The *tetra-acetone hydrazide of ethane tetracarboxylic acid* was prepared in order to confirm the constitution of the above hydrazide. The latter was dissolved in acetone and the solution allowed to evaporate when a sparingly soluble solid was obtained melting at 206°. The air dried product without any further purification, gave on analysis:

0.1402 gram gave 30.5 ccs. of N at 18° and 766.8 mms., N = 23.8 per cent.
$C_{10}H_{30}O_4N_8$ requires N = 26.5 per cent.

In the second series of experiments the reaction was carried out at 100° in sealed flasks. Using 40 grams of dibromide and the corresponding quantity of ethyl sodiomalonate in 150 ccs. of alcohol and heating for 25 hours, the following results were obtained. The alcohol was first distilled off and from the distillate 5 grams of tetrahydrobenzene containing a little dihydrobenzene was obtained. The residue was then worked up in the usual manner and distilled in a vacuum, when two main fractions boiling at 110°—140°/36 mms, and 180°—200°/20 mms. respectively, were obtained. These fractions on redistillation through a column gave a large fraction boiling constantly at 92°/17 mms., a small intermediate fraction and a high boiling point fraction which completely solidified and proved to be practically pure ethane tetracarboxylic ester, yield 7 grams. The lower boiling point fraction could not be resolved by distillation, since the boiling point was quite constant but is was proved to be simply a mixture of

ethyl malonate and dibromo*cyclo*hexane. Thus with dilute alkali the ester was hydrolysed and pure dibromo compound remained unchanged and with alcoholic ammonia in the cold, malonamide and *cyclo*hexene dibromide were readily obtained pure. In this experiment about 5 grams of tar were produced.

In the third series of experiments a still higher temperature was used and although the reaction took another course, it was not the one desired. Dibromo*cyclo*hexane and ethyl malonate in equivalent quantities were added to an equivalent of sodium in amyl alcohol and the mixture heated in an oil bath at 140° for about 30 hours. The reaction product was then worked up as follows. The dark brown liquid was first distilled until the distillate came over at 120°. The latter consisted of ethyl alcohol and a little tetrahydrobenzene, thus the ethyl malonate had been transformed into the corresponding amyl ester. The residue in the distillation flask was boiled with aqueous caustic soda solution for five hours, the amyl alcohol removed in a current of steam and the residual solution extracted with ether. The ethereal extract consisted of unchanged dibromo*cyclo*hexane and some tarry matter. The aqueous solution was then evaporated to a small bulk, acidified and again extracted with ether. The extract after drying over sodium sulphate and removing the solvent, gave an uninviting dark brown semi-solid mass. This on heating to about 210° decomposed with the production of carbon dioxide and a distillate, consisting principally of acetic acid, was obtained. The dark coloured residue in the flask, was then extracted with cold water by which means it was separated into a soluble and an insoluble portion. The aqueous extract on evaporation gave a small quantity of crystalline material, which from its behaviour on heating alone and with resorcinol, contained succinic acid. The yield was so very small however, that it was impossible to separate it into its pure constituents.

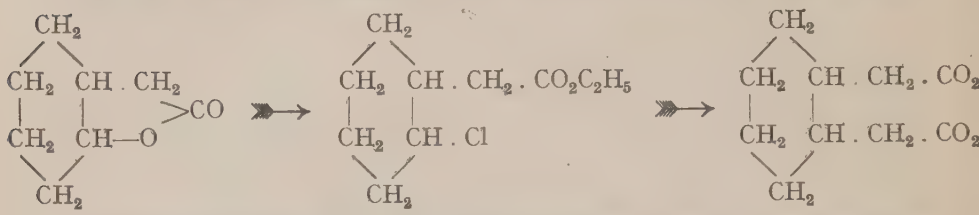
The insoluble portion consisted of a dark brown oil which was easily purified by distillation in a vacuum. This substance proved to be the lactone of *cyclo*hexanol-2-acetic acid or hexahydro-*iso*coumaranone, (2-keto-hexahydrocoumaran). This substance has been prepared in quantity by other methods and will be considered in another section. The yield was 20—30 per cent.

Thus it appears that by elevating the temperature one of the bromine atoms in the dibromide can be replaced in the normal manner by ethyl sodiomalonate. The yield is so poor however, and charring so considerable that it would appear impossible to replace the other bromine atom by using a still higher temperature.

(b) *The interaction of ethyl sodiomalonate and* cyclo*hexene halogenohydrins.*

It was thought possible to prepare *cis-cyclo*hexane diacetic acid from hexahydro*iso*coumaranone if this could be obtained in quantity, by the following series of reactions and therefore the action of ethyl

sodiomalonate on the halogenohydrins of *cyclohexene* was studied with the idea of obtaining a more satisfactory yield of this material.



The chlorohydrin has been prepared by the action of hypochlorous acid on tetrahydrobenzene [1]), and the solid iodohydrin by the action of iodine and yellow mercuric oxide on *cyclo*hexene in moist ethereal solution [2]). The manipulative difficulties experienced in the production of the chlorohydrin and the expense attached to BRUNEL'S method, coupled with the fact that the iodohydrin reacts with ethyl malonate in various ways, made it desirable to try and prepare the hitherto unknown bromohydrin. This was accomplished as follows.

Preparation of cyclohexane 1 : 2 *bromohydrin.* A solution of hypobromous acid was first prepared, by adding 20 grams of yellow mercuric oxide to a litre of water and then 40 grams of bromine and shaking until the reaction was complete (about five minutes). A further quantity of mercuric oxide and bromine was then added and the process repeated until 200 grams of mercuric oxide and 100 grams of bromine had been used. The pale straw coloured solution was then filtered and used immediately. It would appear unnecessary to use twice the theoretical quantity of mercuric oxide as recommended by STARK[3]) but is is not sufficient to use molecular quantities as stated by DANCER [4]).

A litre of the above solution was cooled in ice and 45 grams of tetrahydrobenzene added fairly rapidly with vigourous shaking. Much heat was developed and a heavy oil was produced. The shaking was continued for one hour, the solution saturated with salt and extracted with ether. The etheral extract was subsequently dried over sodium sulphate and distilled on a water bath, first at the ordinary pressure and then under 30 mms. The bromohydrin remained in the distillation flask as an almost colourless, rather viscous liquid. The yield was approximately 70 per cent. Analysis showed that the product was almost pure and therefore it was not purified further. Analysis gave:

0.2562 gram gave 0.3642 gram CO_2, and 0.1420 gram H_2O; C = 38.8 per cent. H = 6.15 per cent. $C_6H_{11}OBr$ requires C = 40.2, H = 6.15. per cent.

In order to prepare this bromohydrin successfully it is essential to follow the above directions as nearly as possible, since it has been

[1]) FORTEY, loc. cit.
[2]) BRUNEL, Ann. chim. phys. (8) **6**, 219—245 (1905).
[3]) Ber. **43**, 672 (1910).
[4]) Ann. **125**, 235 (1863).

found that quite small alterations in the technique of the experiment, such as using a larger concentration of hypobromous acid or less tetrahydrobenzene, cause large quantities of *cyclo*hexene dibromide to be produced. Thus by using one and a half litres of hyprobromous acid solution and 40 grams of *cyclo*hexene, as described above, 100 grams of oil were obtained but the latter contained 80—85 per cent. of the dibromide. It is clear therefore that an excess of the hydrocarbon must be used.

The interaction of cyclo*hexene bromohydrin and ethyl sodiomalonate.*

The bromohydrin reacted very readily with ethyl sodiomalonate giving a good yield of hexahydro*iso*coumaranone. A mixture of 41 grams of ethyl malonate, 41 grams of the crude bromohydrin and sodium ethoxide from 10.2 grams of sodium (2 mols.), in 250 ccs. of absolute alcohol, was heated for one hour on the water bath. The contents of the flask became semi-solid and were then allowed to cool. A large volume of dry ether was then added to complete the precipitation of the sodium compounds, which were filtered, and well washed with alcohol and ether. When dry they weighed 50 grams. On evaporation of the alcohol and ether from the filtrate, an oil was obtained, which on distillation in a vacuum gave 7 grams of a mixture of ethyl malonate and dibromo*cyclo*hexane, 9 grams of unchanged bromohydrin and 5 grams of undistillable matter.

The sodium salts were dissolved in cold water and treated with dilute hydrochloric acid and the heavy oil which separated was extracted with ether. This oil had an extremely pungent odour. The ethereal extract was dried over anhydrous sodium sulphate, the ether distilled off on the water bath and the oil which could not be distilled apparently without undergoing some decomposition, was digested at 80° for half an hour with 120 ccs. of 15 per cent. potash solution. When all had dissolved, the solution was acidified but nothing separated; therefore the solution was carefully evaporated on the water bath to a small volume and the brown oil which gradually separated, extracted with ether. On evaporating the solvent, a dark coloured, semi-solid, non-crystalline mass was obtained, which on heating decomposed with the production of carbon dioxide and an oily substance, which distilled almost completely at 160°—180°/20 mms., leaving only a small amount of non-volatile tar. As was expected this product proved to be hexahydro*iso*coumaranone.

The interaction of ethyl malonate and cyclo*hexeneiodohydrin.*

The iodohydrin for this investigation was prepared according to the original method of BRUNEL [1]) from tetrahydrobenzene, iodine and moist mercuric oxide. The yield of pure product was fairly good.

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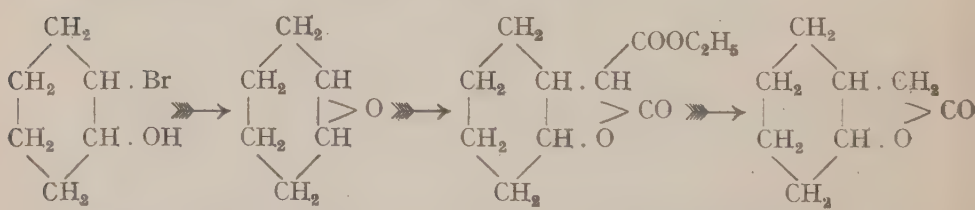
[1]) loc. cit.

Organic iodine compounds usually react with ethyl sodiomalonate more smoothly and give better yields of the desired products than the corresponding bromides or chlorides but this does not appear to be the case with the *cyclo*hexene halogenohydrins. The iodohydrin reacts very readily with ethyl sodiomalonate a reaction being noticed in the cold, but when the reagents are allowed to interact at 80°, although the hexahydro*iso*coumaranone is obtained in appreciable quantities, by products are also produced in large amounts. Thus on heating molecular proportions of the reactants in alcohol, the reaction is at an end in an hour and a half and the mixture becomes semi-solid owing to the precipitation of sodium derivatives. On digesting with aqueous caustic potash, however, and distilling in a current of steam, a large quantity of an insoluble oil which contained iodine was obtained. It was impossible to prove the constitution of this by product, since, owing to an unavoidable accident, it was completely lost. The alkaline solution remaining from the steam distillation, on treatment with acid etc., as previously described, gave pure hexahydro*iso*coumaranone and a rather large proportion of tar.

Thus, as a result of these experiments, it is evident that hexahydro*iso*coumaranone may be prepared fairly easily from the cyclohexene halogenohydrins but the results are not so good as would be desired owing to the simultaneous production of useless by products. During the interaction of the iodohydrin and ethyl sodiomalonate, *cyclo*hexene oxide was detected as an intermediate product. This gave a clue as to the mechanism of the reaction and it has been found that the production of hexahydro*iso*coumaranone from the halogenohydrins takes place in the following stages.



This is proved in the next section and it may be stated here, that this compound is best made in quantity by the interaction of ethyl sodiomalonate and cyclohexene oxide.

(c) *The action of ethyl sodiomalonate on* cyclo*hexene oxide*, — cyclo*hexanol-2-malonic and* cyclo*hexanol-2-acetic acids and their derivatives.*

The *cyclo*hexene oxide used in this part of the investigation was prepared in two ways, the method given by BRUNEL [1]), on the whole being the more easily carried out. In this method an ethereal solution of the iodohydrin is treated in the cold with an excess of pow-

[1]) Ann. chim. phys. (8) **6**, 235 (1905).

dered caustic potash and the oxide obtained pure by fractionating the ethereal solution. The yield averaged about 60 per cent.

The second method, which, apparently, is not described in the literature, is a modification of that due to PRILESCHAÉEFF [1]). A solution of benzoyl hydrogen peroxide in ether, was prepared according to the instructions given by BAEYER and VILLIGER [2]), and the active oxygen estimated by titrating the amount of iodine set free from potassium iodide. The calculated quantity of tetrahydrobenzene was then added and the mixture allowed to remain until a test showed the absence of active oxygen (20 hours). The solution was then washed with caustic soda solution to free it from benzoic acid, dried over anhydrous sodium sulphate and very carefully fractionated. The yield of *cyclo*hexene oxide by this method is quantitative. It should be mentioned also, that in spite of its relatively high boiling point, *cyclo*hexene oxide is extremely volatile and unless the ethereal solution is fractionated with the help of a column, large quantities, as much as 60 per cent., of the oxide may pass over with the ether.

The action of ethyl sodiomalonate on ethylene oxides has been studied by TRAUBE and LEHMANN [3]), who represented the reaction with ethylene oxide and epichlorhydrin as follows:

$$\begin{array}{l} CH_2 \\ | \quad >O + CHNa\,.\,(CO_2C_2H_5)_2 = \\ CH_2 \end{array} \begin{array}{l} CH_2ONa \\ | \\ CH_2\,.\,CH(CO_2C_2H_5)_2 \end{array} \longrightarrow \begin{array}{l} CH_2{-}O \\ | \quad >CO \\ CH_2\,.\,CH\,.\,CO_2C_2H_5 \end{array}$$

the sodium compound passing into the lactone on treatment with dilute acids. HALLER and BLANC [3]) also used this reaction in their synthesis of terebic acid, $\gamma\,\gamma$-dimethyl-$\alpha\,\beta$-dicarbethoxy butyrolactone being prepared from ethyl sodiomalonate and ethyl $\beta\,\beta$-dimethyl glycidate. These investigators also discovered an exception in $\alpha\,\beta\,\beta$-trimethyl glycidate, which would not react with ethyl sodiomalonate. This indifference was ascribed to steric hinderence.

The reaction between *cyclo*hexene oxide and ethyl sodiomalonate was carried out as follows. A solution of ethyl sodiomalonate was prepared from 8.4 grams of sodium, 57 grams of ethyl malonate and 300 ccs. of alcohol and cooled below 20°, when 33 grams of the oxide were added. The reaction does not take place in the cold, with the development of heat as is the case with ethylene oxide but on warming to 70° for half an hour, the whole mass very suddenly became semi-solid owing to the crystallisation of sodium compounds. The heating was continued for one hour longer, the reaction mixture allowed to cool and the sodium compounds filtered at the pump in order to free them as much as possible from alcohol. Owing to the gelatinous

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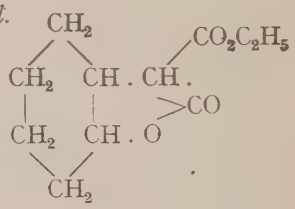
[1]) Ber. **42**, 4811; J. Russ. Phys. Chem. Soc. **42**, 1387, 1418 (1910); **43**, 609 (1911).
[2]) Ber. **33**, 1569 (1900).
[3]) Ibid. **32**, 720 (1899); **34**, 1971 (1901).
[4]) Compt. rend. **142**, 1471 (1906).

nature of the product, however, this operation was only partially successful. The alcoholic filtrate contained nothing but a small amount of dissolved sodium compounds. The latter were then suspended in water, decomposed with dilute acid and the oily product extracted with ether. The ethereal extract was dried and distilled on the water bath, first at ordinary pressures to remove the ether and finally at 10 mms. pressure to remove the small quantity of alcohol.

The lactone of cyclo*hexanol-2-carbethoxy acetic acid.*



In this way 50 grams of a pale yellow, somewhat viscous oil was obtained, which the analysis and reactions proved to be the lactone of *cyclo*hexanol-2-carbethoxy-acetic acid. It was impossible to purify it further, however, since it could not be induced to crystallise and on distillation it boiled at 190°-200°/10 mms. with much decomposition. Analysis gave

0.2120 gram gave 0.4806 gram of CO_2, and 0.1460 gram of H_2O.
C = 61.81 per cent., H = 7.65 per cent.
$C_{11}H_{16}O_4$ requires C = 62.27 per cent., H = 7.55 per cent.

Cyclo*hexanol-2-malonamide*, $C_6H_{10}<\begin{matrix}CH\,.\,(CONH_2)_2 & (2)\\ OH & (1)\end{matrix}$

The crude lactone (2 grams) was dissolved in an excess of alcoholic ammonia and left for two days, when a white granular crystalline product separated. The *cyclo*hexanol-2-malonamide thus obtained was filtered and washed with alcohol. The crystals were hard and insoluble in all the commoner organic solvents with the exception of boiling glacial acetic acid, which decomposed it. The amide melted at 227°-228° (corr.) with violent gas evolution and was slowly hydrolysed by boiling sodium carbonate solution. It was not an ammonium salt since it was unchanged by cold dilute hydrochloric acid.

On analysis: 0.1774 gram gave 21.2 ccs. of N at 750.2 mms. and 16°.
N = 13.7 per cent., $C_9H_{16}O_3N_2$ requires N = 14.00 per cent.

The lactone of *cyclo*hexanol-2-carbethoxyacetic acid reacted with hydrazine hydrate in two ways according to the conditions of the experiment.

Cyclo*hexanol-2-carbethoxyacethydrazide*, $C_6H_{10}<\begin{matrix}CH<\begin{matrix}COOC_2H_5\\ CO.NH.NH_2\end{matrix}\\ OH\end{matrix}$,

may be prepared as follows. The lactonic ester, (2 grams), was dissolved in 20 ccs. of alcohol and 10 drops of 90 per cent. hydrazine hydrate solution added. On shaking, the mixture became warm and almost instantly set to a crystalline mass. After standing for five minutes the product was filtered, washed and recrystallised from 40 parts of ordinary alcohol. It separated from this solvent in a felted mass of silky needles melting at 184°-185° (corr.) with decompo-

sition, after sintering at about 175°. The melting point was quite definite when the substance was rapidly heated but on slow heating somewhat erratic results were obtained. The hydrazidic nature of the substance was demonstrated by its reaction with acetone to give a compound melting with decomposition at 160°-165° and by its solubility in cold alcohol containing a little benzaldehyde. On analysis,

0.1772 gram gave 17.3 ccs. of N at 8° and 772.0 mms.
N = 11.92 per cent. $C_{11}H_{20}O_4N_2$, requires N = 11.80 per cent.

showing that the substance had the constitution given above. Thus under these conditions the lactone ring is opened with great ease leaving the ester group intact.

Cyclo*hexanol-2-malonhydrazide*, $C_6H_{10}<\begin{matrix}CH\,.\,(CO\,.\,NH\,.\,NH_2)_2\\OH\end{matrix}$, is obtained by heating the ester lactone, or the hydrazide described above, with an excess of hydrazine hydrate in absolute alcohol for two to three hours. The dihydrazide, which is very sparingly soluble, separates as a white crystalline powder melting at 226°-227° (corr.) after softening at 224°. On analysis,

0.1242 gram gave 25.2 ccs. of N at 18° and 766.4 mms.
N = 23.67 per cent., $C_9H_{18}O_3N_4$, requires N = 24.35 per cent.

The constitution of the sodium compounds produced by the action of ethyl sodiomalonate on cyclo*hexene oxide.*

The reaction between these two substances according to TRAUBE and LEHMANN [1]), leads to the production of an alcoholate of the type (I) but as far as can be ascertained no proof is given as to where the sodium atom really is and since it may be present as a "sodiomalonate", as represented in (II), or even as the sodium salt of an acid (III), the following experiment was tried in order to settle the constitution of the sodium derivatives. The sodium compound was suspended in absolute alcohol and an excess of ethyl iodide and the whole boiled for six hours. The unchanged sodium compounds were filtered, the alcohol destilled off and the pale yellow oil extracted from the dissolved sodium iodide with dry ether. This pale yellow oil was examined as follows.

$>C\,.\,ONa$ $>C\,.\,OH$ $>C\,.\,OH$
$>C\,.\,CH\,.\,(CO_2C_2H_5)_2$, $>C\,.\,CNa\,.\,(CO_2C_2H_5)_2$, $>C\,.\,CH<\begin{matrix}CO_2Na\\CO_2C_2H_5\end{matrix}$
(I). (II). (III).

(*a*) *Action of ammonia.*

On leaving the oil, (2 grams), in a strong solution of absolute alcoholic ammonia for two days, a small quantity (0.2-0.3 gram), of

[1]) loc. cit.

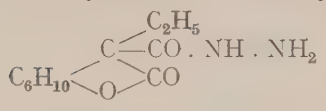
a white crystalline solid was obtained, which from its characteristic appearance and melting point, 226°-227°, proved to be *cyclo*hexanol dimalonamide. The mother liquors on evaporation gave a mixture consisting of at least two components but neither could be obtained in a pure condition.

(*b*) *Action of hydrazine.*

The crude oil was heated with an excess of an alcoholic solution of hydrazine hydrate for twenty minutes, cooled and the sparingly soluble product filtered. This proved to be *cyclo*hexanol dimalonhydrazide, melting at 226°-227°, which on analysis gave the following result.

0.1432 gram gave 30.7 ccs. of N at 24° and 763.6 mms.,
N = 24.03 per cent. calc., N = 24.3 per cent.

On evaporation, the mother liquors yielded a "glue", which refused to solidify but on dissolving twice in water and again evaporating the solution, a solid product was obtained. This substance on recrystallisation from alcohol, melted at 220°-225° (uncorr.) with decomposition and the analysis showed that in all probability it was the hydrazide of α-ethyl-α-carboxy-hexahydro*iso*coumaranone, shown in the annexed formula, which could only occur if the sodium compound corresponding to (II) were present. The analytical results were



0.1300 gram gave 14.5 ccs. of N at 21° and 762.4 mms.,
N = 12.65 per cent., $C_{11}H_{18}O_3N_2$, requires N = 12.39 per cent.

(*c*) *Hydrolysis.*

The ethylated product was boiled for some time with alcoholic potash, evaporated to a small bulk, acidified and extracted with ether. The extract on distilling off the solvent, gave a *semi-solid* mass quite different from the oily product obtained on the hydrolysis of α-carbethoxy-hexahydro*iso*coumaranone (see later). A solid malonic acid was obtained from this mass but the quantity available was insufficient to allow of its constitution being established.

The production of *cyclo*hexanol malonamide and dimalonhydrazide from this ethylated mixture can be satisfactorily explained only by assuming that the product formed by the action of ethyl sodiomalonate on *cyclo*hexene oxide, contains some sodium compound having a constitution represented by (III), whilst the second hydrazide can only be obtained from a sodium compound having a structure represented by (II). Assuming therefore, that the reaction between ethyl sodiomalonate and *cyclo*hexene oxide takes place in an identical manner with the reaction studied by TRAUBE and LEHMANN, there appears to be no justification for representing this reaction as shown on page 19, since the sodium compounds obtained are represented in part by the

constitutions (II) and (III) above. In fact, in the experiments just described, no evidence was forthcoming in support of the alcoholate formula usually assigned to these sodium compounds in the text books.

Hydrolysis of α-carbethoxy hexahydroisocoumaranone.

When the ester lactone (42 grams), was added to 400 ccs. of 10 per cent. alcoholic potash solution, warmed to 60°, a vigorous reaction took place and normal potassium *cyclo*hexanol malonate, was precipitated. The solution was boiled to complete the reaction and the potassium salt filtered. Two analyses, one (A), on the air dried substance and one (B), dried in a dessicator were made.

(B) 0.2135 gram gave 0.1425 gram K_2SO_4, K = 28.78 per cent.
(A) 0.2462 gram gave 0.1483 gram K_2SO_4, K = 27.02 per cent.
$C_6H_{10}<^{OH}_{CH:(COOK)_2}$ requires K = 28.06 per cent.

This normal salt was apparently stable in the dry state but not in solution. It was extremely soluble in water giving a weakly alkaline solution, the alkalinity of which increased on keeping or boiling, owing no doubt to the production of free caustic potash, by hydrolysis and the closing of a lactone ring. As a consequence of this dissociation it was impossible to obtain other normal salts by precipitation from this solution, the salts so obtained being invariably contaminated with metallic oxides. Thus the silver salt precipitated from this solution contained 56.00 per cent. of silver instead of 51.82 per cent. These normal salts were obtained in another way described in the following section.

On acidifying the potassium salt solution and extracting with ether, *α-carboxy hexahydroisocoumaranone* was obtained as a rather viscous oil, which could not be induced to crystallise.

*Hexahydro*isocoumaranone *and derivatives of* cyclo*hexanol-2-acetic acid.*

As already described hexahydro*iso*coumaranone or the lactone of *cyclo*hexanol acetic acid, may be obtained in a great variety of ways, all of which depend of the production of *cyclo*hexanol malonic acid but by far the most efficient way of preparing this compound is as follows.

Tetrahydrobenzene oxide, (30 grams), was allowed to react with an equivalent of ethyl sodiomalonate in 250 ccs. of alcohol as already described. When the reaction was at an end, sufficient water was added to dissolve the sodium compounds and the mixture heated under a reflux for one hour. The alcohol was then distilled off on a brine bath and the aqueous solution remaining, evaporated to about 200 ccs. In this way a neutral solution was obtained containing the sodium salt of α-carboxy-hexahydro*iso*coumaranone, or what seems to be more likely from the experimental results, of *cyclo*hexanol malonic acid, since, strange to say, on treating this monosodium salt solution

with silver nitrate solution or with solutions of other salts of the heavy metals, the normal salts of *cyclo*hexanol malonic acid are precipitated. Thus silver *cyclo*hexanol malonate, which cannot be obtained from a solution of the dipotassium salt, (see page 23), is readily obtained as a white sparingly soluble crystalline solid. Its constitution was clearly proved by analysis.

0.2380 gram gave 0.1214 gram of Ag. Ag = 51.01 per cent.
$C_9H_{12}O_5Ag_2$ requires Ag = 51.80 per cent.

The sodium salt solution was acidified with sulphuric acid and the acid lactone extracted with ether. The pale brown oil obtained on evaporating the solvent was then gradually heated in an oil bath to 220° when a vigorous evolution of carbon dioxide took place in the neighbourhood of 200° and very suddenly ceased. During this decomposition nothing but a minute quantity of acetic acid should distil but if the heating has been too rapid some of the lactone may pass over also. When the evolution of gas had ceased the oily residue was distilled in a vacuum and the crude lactone passed over at 135°-142°/15 mms. or 148°-154°/28 mms., leaving only a very small amount of tar in the distillation flask. The product thus obtained is practically pure and may be freed from the small amount of impurity it contains by redistillation, either at the ordinary pressure or in a vacuum.

*Hexahydro*isocoumaranone or the lactone of *cyclo*hexanol acetic acid, is a colourless, fairly mobile liquid possessing a faint but characteristic odour. The following constants were determined.

Boiling point 152°—153°/28 mms., 138°—139°/15 mms. and 262.5°—263.5°/765 mms. (uncorr.)

$D_4^{12.5} = 1.0925$, $n_D^{12.5} = 1.4790$, $M_D = 36.36$ calc. = 36.48.

When sufficiently cooled the pure substance freezes to a mass of white needles; the melting point and freezing point when determined by the method of cooling, using about five grams of substance, are identical, namely -5.5°, thus indicating the purity of the sample investigated. The analysis gave

0.2042 gram gave 0.5132 gram of CO_2 and 0.1558 gram of H_2O.
C = 68.54 per cent. H = 8.48 per cent.
$C_8H_{12}O_2$ requires C = 68.57 per cent. H = 8.57 per cent.

Hexahydroisocoumaranone has all the characteristic properties of a simple lactone, being insoluble in water or sodium carbonate solution but dissolving gradually, especially on warming, in caustic soda. A quantitative experiment using an excess of potash and back titrating with N/10 acid, gave an equivalent for the lactone of 163, against 140 demanded by theory, thus showing the remarkable ease with which lactone formation takes place.

Cyclo*hexanol-2-acetic acid*, $C_6H_{10}\begin{matrix}CH_2 \cdot COOH \\ OH\end{matrix}$, *and its salts.*

Solutions of potassium *cyclo*hexanol acetate gave a clear solution on acidification which deposited the lactone on warming. Since the

latter is but sparingly soluble in water, this solution must contain *cyclo*hexanol acetic acid but all attempts to obtain the acid from such solutions by crystallisation or extraction failed, the lactone being obtained in each case. Unexpectedly, it was found that the lactone dissolved in dilute hydrobromic acid on warming, the lactone ring opening to form *cyclo*hexanol acetic acid but such a solution, even on spontaneous evaporation gave only the unchanged lactone.

Potassium cyclo*hexanol acetate.* When the lactone was treated with an excess of absolute alcoholic potash, the solution became hot and after boiling for a little time a solid separated. Enough boiling absolute alcohol was now added to complete solution and on cooling, the potassium salt crystallised in shining platelets. On analysis

0.5519 gram gave 0.2456 gram of K_2SO_4, K = 19.95 per cent.
$C_8H_{13}O_3K$ requires K = 19.89 per cent.

Silver cyclo*hexanol acetate* is readily obtained by adding a solution of silver nitrate to a solution of the above potassium salt. On analysis

0.3140 gram gave 0.1306 gram of silver, Ag = 41.59 per cent.
$C_8H_{13}O_3Ag$ requires Ag = 40.8 per cent.

Cyclo*hexanol acetic acid* was obtained from the potassium salt by treatment with dry hydrogen chloride in ice cold absolute ether. The solution was then filtered from the precipitated potassium chloride and evaporated at the ordinary temperature in a current of dry air, when a viscous oil was obtained. This oil on leaving for some time in the ice chest, became partly crystalline. The solid was then freed from oily matter in a press and quickly washed with ether when it melted at 90°—95°. On cautious crystallisation from this solvent a solid was eventually obtained melting at 97°—102° when rapidly heated. There seems to be no doubt that this substance was impure *cyclo*hexanol acetic acid since it was readily converted into the lactone on melting. It was unstable in aqueous solution, from which only the lactone could be recovered and a direct titration with caustic soda gave a molecular weight of 180 instead of the theoretical value 158. It would therefore appear that the acid has such strong tendencies to pass into the lactone that it does so to a great extent in aqueous solution.

Cyclo*hexanol-2-acetamide*, $C_6H_{10}\begin{matrix}CH_2 \cdot CONH_2\\OH\end{matrix}$.

This very characteristic derivative was prepared by heating the lactone for four hours at 100° with alcoholic ammonia. On evaporation of the solvent a theoretical yield of the hydroxyamide was obtained as a mass of colourless needles. *Cyclo*hexanol acetamide is very soluble in water, alcohol and acetone but sparingly soluble in petroleum, ether or benzene. Its crystalline habit is very characteristic and it may be crystallised from a mixture of equal parts of acetone and water in clear stout prisms which are several millimeters long and are always grouped in clusters. The melting point is 154° (corr.).

0.1654 gram gave 12.7 ccs. of N at 18° and 774.6 mms.
N = 9.04 per cent. $C_8H_{15}O_2N$ requires 9.04 per cent.

The amide is extremely stable towards heat and may be distilled without undergoing any change. There was no indication of the formation of hexahydrooxindole.

Cyclo*hexanolacethydrazide*, $C_6H_{10}<^{CH_2 \cdot NH \cdot NH_2}_{OH}$, was also prepared by boiling a 10 per cent. solution of the lactone in alcohol with hydrazine hydrate for five minutes. On cooling the hydrazide separated and on recrystallisation from water it was pure. This derivative crystallises in a felted mass of silky needles melting at 167.5° (corr.). On analysis

0.1344 gram gave 18.9 ccs. of N at 14° and 762.0 mms. N = 16.50 per cent.
$C_8H_{16}O_2N_2$ requires N = 16.30 per cent.

Cyclo*hexanol acetbenzhydrazide*, was also prepared by boiling the above hydrazide with an alcoholic solution of benzaldehyde for a few moments and allowing to crystallise. It separates in colourless, feathery needles, melting at 173°-174° (corr.). On analysis

0.1732 gram gave 15.8 ccs. of N at 16° and 767.7 mms. N = 10.70 per cent.
$C_{15}H_{20}O_2N_2$ requires N = 10.77 per cent.

Cyclo*hexanol acetphenylhydrazide*, $C_6H_{10}<^{CH_2 \cdot CONH \cdot NHC_6H_5}_{OH}$.

This was also a very well defined derivative and was prepared by heating the lactone with an excess of phenylhydrazine on the water bath for two hours. The solid product was then crystallised twice from alcohol, when it was obtained in small colourless crystals melting at 165.5° (corr.). An analysis gave the following result:

0.1622 gram gave 16.0 ccs. of N at 14° and 759.0 mms., N = 11.53 per cent.
$C_{14}H_{20}O_2N_2$, requires N = 11.30 per cent.

The action of phosphorus pentachloride on the lactone of cyclo*hexanol acetic acid.*

The reaction between lactones and phosphorus pentachloride appears not to have been studied systematically but BENTLEY, HAWORTH and PERKIN [1]) showed that α-methyl butyrolactone gave γ-chloro-α-methyl butyryl chloride. From analogy it was thought possible therefore, to convert the above lactone into 1-chloro*cyclo*hexane-2-acetyl chloride, $C_6H_{10}<^{CH_2 \cdot COCl}_{Cl}$, in a similar manner.

Phosphorus pentachloride, (30 grams), was carefully added to the lactone (25 grams) and the mixture gently warmed on the water bath when a reaction took place, the phosphorus halide gradually dissolving and a relatively large proportion of hydrogen chloride being evol-

[1]) J. Chem. Soc. **69**, 161 (1896).

ved. In half an hour the reaction was apparently at an end and the mixture was heated one hour longer and left over night. The brown liquid was then distilled in a vacuum from a boiling water bath to free it from phosphorus oxychloride and since the residue could not be distilled without much decomposition, the product was poured into absolute alcohol to convert the crude acid chloride into the corresponding ester. The alcoholic solution, which became warm on mixing, was boiled for one hour, the alcohol distilled off and the residual oil distilled in a vacuum when the following fractions were obtained: (a) 110°-150°/10 mms., (b) 150°-230°/10 mms. with some decomposition. Fraction (a) on redistillation was collected in three portions, which had the following constants.

115°—120°/20 mms. $n_D = 1.4710$; 116°—120°/9 mms. $n_D = 1.4765$; 120°—125°/9 mms. $n_D = 1.4792$.

This product in boiling point and refractive index, had a very strong resemblance to the original lactone. The oil also reacted acid and contained free hydrogen chloride, from which it was easily freed, however, by allowing it to remain for two days in a vacuum over caustic soda.

The neutral product so obtained contained 10 per cent. of chlorine and was therefore a mixture of the original lactone and chloro*cyclo*hexyl acetic ester which contains 17 per cent. of chlorine. The mixture was then treated in the cold with 40 per cent. alcoholic hydrogen chloride for 24 hours and again fractionated in the hope that the yield of the chloroester would be increased. The product so obtained, however, boiled at 130°—140°/20 mms. or at 225°—240°/764 mms. and analysis showed that it contained about 12 per cent. of chlorine. Thus the final product was still a mixture and the nearness of the boiling points of the two constituents made separation impossible. [1]) The mixture was used in the following experiment.

Attempts to replace the chlorine in the chloroester by the group $CH_2 . COOH$ by the malonate reaction failed. No sodium chloride was formed when the mixture was heated with alcoholic ethyl sodiomalonate in a sealed tube at 100° for 24 hours and on heating to a higher temperature a reaction slowly took place but it was of a complex nature, none of the desired compound being detected on hydrolysis and a very large proportion of tarry material being produced.

(d) Ortho-phenylene diacetic acid and its derivatives.

The synthetic experiments with tetrahydrobenzene derivatives having failed to yield *cyclo*hexane diacetic acid, it was resolved to try to obtain it by reducing the corresponding aromatic acid, *o*-phenylene diacetic acid. This is most readily obtained from *o*-xylene though $\omega\omega'$-

[1]) A perusal of the physical constants of the γ-chloroesters and the corresponding lactones already described in the literature, shows that they are very similar in the two cases, hence the difficulty in separating the constituents of the above mentioned mixture.

o-xylene dibromide and the corresponding nitrile but, since the former is now unobtainable in quantity from the usual trade sources, it was thought desirable to search for some other means of preparing it. The only other source available appeared to be dihydronaphthalene and it has been obtained from this compound by BAMBERGER and LODTER [1]) and by Leroux [2]). In each case the method of preparation depends on the oxidation of tetrahydronaphthalene-diol the two methods differing only in the method of obtaining the latter, which is then treated with chromic acid. In neither case is any yield stated although the yield of diol according to BAMBERGER and LODTER is very poor. On repeating LEROUX's experiments it was found that the preparation of the diol by this method was extremely laborious and since on oxidation with chromic acid, naphthaquinone and more complex substances are formed together with homophthalic acid, which proves to be difficult to separate from the *o*-phenylene diacetic acid, this method was abandonned. Direct oxidation of dihydronaphthalene with chromic acid was also useless.

Ozonisation of dihydronaphthalene.

An account of the action of ozone on dihydronaphtalene could not be found in the literature and since it was considered that the ozonide might give *o*-phenylene diacetic acid on fission with water and further oxidation in the usual manner, the following experiments were carried out. It will be seen that dihydronaphthalene readily gives a monoozonide but it proved to be so extremely stable that it was impossible to obtain any definite fission product.

The dihydronaphthalene for this and the above experiments was conveniently prepared by reducing naphthalene with sodium and boiling absolute alcohol according to the directions of ERDMANN [3]). The crude product boiling at 211°—213° was used. The addition of iodine in LEROUX's experiments showed that it contained between 80 and 90 per cent. of dihydronaphthalene; this was also confirmed by the ozonisation experiments. The ozonisation was carried out as follows.

The hydrocarbon (7 grams) was dissolved in 20 ccs. of dry carbon tetrachloride and cooled in a freezing mixture. A stream of purified ozonized air containing approximately 45 mgs. of ozone per litre [4]) was passed through the solution at the rate of 10—12 litres per hour. The ozone was completely absorbed until the whole of the unsaturated hydrocarbon had reacted; this required 55 litres showing that the dihydronaphthalene was of the order 85 per cent. pure. After the absorption, the ozonide floated on the surface of the carbon tetrachloride. The latter was easily decanted and the product washed several times by decantation with fresh quantities of solvent. The ozonide was finally freed from traces of the solvent by heating it in a vacuum at 30°.

[1]) Ann. **288,** 75 (1895).
[2]) loc. cit.
[3]) VANINO, Handbuch der präparatieven Chemie, II, 362, Stuttgart 1914.
[4]) Cf. NOORDUYN, Diss. Leiden p. 16 (1918).

Dihydronaphthalene mono-ozonide is a colourless, amorphous, somewhat gummy solid insoluble in ether, petroleum, chloroform, carbon tetrachloride or glacial acetic acid. When boiled in the latter it melts and forms a heavy, colourless oil which resolidifies on cooling to an amorphous mass; apparently no decomposition takes place during this procedure. The ozonide may be heated to a fairly high temperature and then it explodes.

This ozonide is remarkably stable to boiling water and is for the most part unchanged when boiled with water for ten hours. On protracted boiling a brown syrup is obtained which shows none of the usual reactions for aldehydes. Although several attempts were made in various ways to obtain *o*-phenylene diacetic acid from this readily accessible product they invariably failed.

Having failed to produce this acid in quantity it was necessary to have recourse to the usual method from *o*-xylene. The latter was converted into dibromo-*o*-xylene by the method described by PERKIN [1]) and this was converted into the corresponding nitrile by adding the powdered bromide (100 grams) to a solution of 60 grams of potassium cyanide in 400 ccs. of 70 per cent. alcohol. The solution was kept near its boiling point and the bromide added in small quantities during one hour. The nitrile was then precipitated with water, extracted with ether, the extract dried over calcium chloride and decolourising charcoal, which absorbed a large amount of the tarry material and the product crystallised first from ether and then from methyl alcohol. The yield of pure cyanide was about 60 per cent [2]).

The *o*-phenylene diacetic acid was obtained from the cyanide by heating it with concentrated hydrochloric acid under pressure [3]) but owing to this method being unsuitable for larger quantities the method of MOORE and THORPE was subsequently used. In their communication these authors state that they obtained a 90 per cent. yield of *o*-phenylene diacetamide. Although, as far as can be seen, the directions given in their paper have been carried out, the main product so obtained, proved to be *o*-phenylene diacetic acid mono-amide.

This being the case it seems advisable to describe this experiment in more detail. The nitrile, (30 grams), was finely powdered and added to 150 ccs. of ordinary concentrated sulphuric acid during 20 mins. The nitrile dissolved to a brown solution and a considerable rise in temperature took place; this was checked however, by external cooling so that it did not rise above about 60°. The solution was then cooled in water and left overnight; it was then poured into 350 ccs. of water and an excess of concentrated ammonia solution added gradually during one hour. The solution became hot and on cooling only 7 grams of crude *o*-phenylene diacetamide separated. This was

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[1]) J. Chem. Soc. **53**, 5 (1888).
[2]) Cf. BAEYER and PAPE, Ber. **17**, 447 (1884); MOORE and THORPE, J. Chem. Soc. **93**, 175 (1908); PERKIN and TITLEY, ibid. **121**, 1563 (1922).
[3]) Cf. Ber. **49**, 2647 (1916).

recrystallised from water and separated in the characteristic, long, silky, asbestos like needles described by MOORE and THORPE.

The filtrate, about 500 ccs., was acidified with dilute sulphuric acid and a thick white precipitate was formed which was filtered, washed and dried. It then melted at 196°—198°. It was sparingly soluble in most solvents but could be recrystallised from large quantities of boiling water or alcohol. After three crystallisations from water and alcohol alternately, the melting point was constant.

O-phenylene diacetic acid mono-amide, $C_6H_4 < \begin{matrix} CH_2CONH_2 \\ CH_2COOH \end{matrix}$ crystallises in small brilliant needles or prisms melting at 207°—208° (corr.). Its reactions clearly proved that it is both an acid and an amide and an analysis gave

0.1816 gram gave 11.3 ccs. of N at 14° and 766.7 mms. N = 7.35 per cent.
$C_{10}H_{11}O_3N$, requires N = 7.25 per cent.

The *o*-phenylene diacetic acid was readily obtained from these amides by hydrolysing them with 10 per cent. caustic potash, boiling with charcoal and acidifying. The crude acid was then purified by repeated crystallisation from dilute hydrochloric acid and boiling the solution with a little charcoal. The pure acid crystallised in large colourless needles melting at 151.5° (corr.).

(*e*) *The reduction of o-phenylene diacetic acid.*

Attempts were first made to reduce this acid by means of sodium and alcohol: one part of the acid was dissolved in twenty parts of carefully dried absolute alcohol and three parts of sodium were added all at once. After the reaction had ceased the solution was acidified, evaporated to dryness and the acid which was extracted with ether was again submitted to the same treatment. Even after this vigorous treatment, however, the original acid was quantitatively recovered unchanged.

The experiment was then repeated using boiling amyl alcohol and sodium but this powerful reagent had no action whatever on the acid. It was then decided to try platinum and hydrogen and at first these experiments failed.

The work of WILLSTÄTTER and his collaborators [1]), however, has definitely proved that the absolute purity of the reactants is essential, the reduction being totally inhibited by mere traces of impurities, which usually occur in aromatic compounds made from coal tar products. Striking examples are the reduction of benzoic acid and naphthalene. [2]) It was therefore decided to purify the materials further. The acid was repeatedly recrystallised from dilute hydrochloric acid

[1]) WILLSTÄTTER and HATT Ber. **45**, 1471 (1912); WILLSTÄTTER and JAQUET ibid. **51**, 767 (1918).
[2]) WILLSTÄTTER and HATT loc. cit.

and finally from water. After six recrystallisations it was possible to reduce it and further recrystallisation appeared to be without effect on either the velocity of the reduction or the character of the product produced.

The platinum black was prepared precisely according to the directions given by WILLSTÄTTER and HATT and it was used as soon as possible (two days) after preparation [1]).

The acetic acid was also purified by distillation and freezing and the hydrogen was purified by the usual method [2]) and stored in an all glass gas holder.

The reduction was carried out under various conditions but the best method was as follows.

The *o*-phenylene diacetic acid (6 grams) along with acetic acid (30 ccs.) and platinum black (2 grams) was introduced into a flask (500 ccs.) fitted with a gas inlet tube reaching to the bottom and carrying a three way tap and a gas outlet tube, which was also closed by a tap. These two tubes were fused into the neck of the flask, the latter being closed with a well fitting glass stopper. The three way tap was connected to a calcium chloride drying tube sealed on to the glass hydrogen gas holder by means of the shortest possible length of specially cleaned rubber pressure tubing and to a cylinder of "pure" compressed air. Before the experiment, air was passed through the mixture in the flask, the three way tap was then closed and the absorption vessel evacuated, Hydrogen was then carefully introduced from the gas holder and the absorption vessel shaken. The absorption took place fairly rapidly at first but gradually slowed down in the course of the day. Next day the absorption vessel was again exhausted and the platinum again activated with air and the experiment recommenced. The whole procedure was repeated daily until the absorption ceased. This usually required about 30 hours and three activations. The absorption stopped quite abruptly when about 10 per cent. more than the theoretical quantity of hydrogen had been absorbed. During the reduction the sparingly soluble *o*-phenylene diacetic acid gradually dissolved in the acetic acid and as the reaction continued a new acid crystallised.

After the reduction, the mixture was heated to dissolve the acid, which had crystallised out and the acetic acid solution filtered from the platinum. The reduction product was recovered from this solution on evaporation as a very pale brown crystalline solid, which generally melted at about 148°. The yield was quantitative and the product on titration proved to be hexahydro-*o*-phenylene acetic acid. Thus

0.1613 gram neutralised 16.14 ccs. of 0.1 N. NaOH Equiv. = 100 (calc.) = 100.

Subsequent experiments have shown that this product is in all probability a mixture of the two possible *cis*- and *trans*- modifications

[1]) WILLSTÄTTER and HATT loc. cit.; see also SKITA, Über katalytische Reductionen organischer Verbindungen, Stuttgart, 1914 p. 9.

[2]) SKITA loc. cit.

of this acid but the separation has proved to be extremely difficult. Thus the product after one crystallisation from water melts quite sharply at 152°—153° and on recrystallisation several times from either water or ethyl acetate, the two most suitable solvents, this melting point remained unchanged. It was therefore assumed at first that this product was a pure individual acid. It would now appear, however, more correct to consider it as either a definite double compound of the *cis* and *trans* acids, which are formed in the reduction in just the correct proportions for its formation or as a eutectic of the same components.

When, however, the crystallisation was carried out very slowly from water or ethyl acetate, the acid separated in quite large shining crystals and the melting point very slowly increased until after some 12 recrystallisations it had reached 163° (corr.) and could not be increased further. This acid on analysis gave,

0.1092 gram neutralised 10.80 ccs. of 0.1015 n.NaOH, Equivalent = 99.6
0.1628 „ „ 16.04 „ „ „ „ „ 100

The silver salt was prepared by adding silver nitrate to a neutral solution of the sodium salt, formed a white crystalline precipitate.

0.0915 gram gave 0.0467 gram of silver, Ag = 51.03 per cent.
0.1348 „ „ 0.0691 „ „ „ „ 51.25 „ „
$C_{10}H_{14}O_4Ag_2$ = 52.2 per cent., $C_{10}H_{14}O_4Ag_2 . 1/2\ H_2O$ = 51.06 per cent.

A neutral solution of the sodium salt gave no precipitate with solutions of calcium or barium chlorides, a semi-gelatinous precipitate with lead acetate and an insoluble deep blue crystalline powder with copper salt solutions.

Evidence of anhydride formation.

The following experiments were carried out with a view to discover whether this acid was capable of giving an anhydride having the properties of deoxycantharidin.

In the first place it was found that distillation in a vacuum caused the melting point to *decrease* some three degrees but the acid was recovered unchanged on treatment with caustic soda and acidifying.

A larger quantity of a slightly impure sample, melting at 156°—159°, was heated for 5 hours at 200° and then distilled in a vacuum when it passed over at 240°/15 mms. The melting point of the distillate was depressed to 142°—147° and on titration its equivalent showed that it contained anhydride. The solid mass was then powdered and extracted with very dilute sodium bicarbonate solution, when a small quantity of a colourless sticky mass, which dissolved only very slowly, was extracted with ether. On evaporating the solvent a solid melting at 142°—146° was obtained. The sodium bicarbonate solution on acidification gave an acid (equivalent = 100.3), melting at 152°—153°. The product melting at 142°—146° was also dissolved in sodium carbonate solution and the acid recovered. The latter melted at

151°--153° (uncorr.) but on crystallisation three times from ethyl acetate it was obtained in the characteristic form melting at 162°—163° (corr.), identical with the product obtained by the laborious fractional crystallisation of the crude reduction product.

Further proof of anhydride formation was obtained by heating a sample of the acid (m.p. 157°—159°) with acetyl chloride. During two hours hydrogen chloride was evolved and then ceased. The acetyl chloride was then distilled off under reduced pressure, the residue left over lime in a vacuum dessicator and finally heated to 130° for a few minutes to free it completely from volatile matter. The residue melted at 146° -147° (uncorr.) after sintering at 141° and on titration

0.1217 gram neutralised 12,85 ccs. of 0.1006 N. NaOH. Equivalent = 94.1 which corresponds to 66 per cent. anhydride.

Attempts to purify this anhydride invariably failed owing no doubt to the instability of such a seven ring structure.

These experiments definitely prove, however, that the small quantity of acid isolated in a pure condition from the crude reduction product gives an anhydride fairly easily, although it is far less stable and less readily formed than those containing five atom rings.

This acid and its anhydride, however, are not identical with deoxycantharidic acid and deoxycantharidin respectively, for the following reasons.

(a) The melting point of the pure acid is 162°—163°, deoxycantharidic acid melts at 160°—165°.

(b) The silver salt of *cis*-cyclohexane 1 : 2 diacetic acid crystallises with half a molecule of water while silver deoxycantharidate crystallises with one molecule.

(c) The greatest difference between the two compounds however is shown in their behaviour on steam distillation. Thus the characteristic of deoxycantharidic acid is its conversion into deoxycantharidin, which passes over into the distillate, when it is distilled in a current of steam. On the other hand, neither the crude reduction product from *o*-phenylene diacetic acid, nor the pure *cis*-acid, nor the mixture consisting of more than two thirds of anhydride is at all volatile under these conditions.

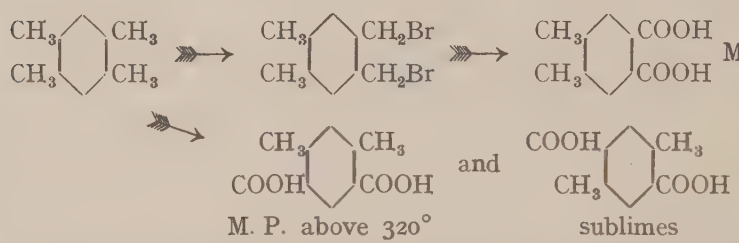
Gadamer's second formula.

If the second formula suggested by GADAMER for cantharidin be correct, then deoxycantharidinic acid will be *cis*-hexahydro-4 : 5 dimethyl phthalic acid and deoxycantharidin the corresponding anhydride.

Obviously, the easiest way to obtain this compound would be to reduce the corresponding aromatic acid, 4 : 5 dimethyl phthalic acid. A perusal of the literature showed that this acid has never yet been prepared in quantity but VON KORCZYNSKI [1]) claims to have prepared a very small amount as follows. He found that when durene was

[1]) Ber. **35**, 871 (1902).

brominated under certain conditions a small quantity, 0.8 gram from 12 grams of durene, of a durylene dibromide melting at 157° was obtained. This was converted into the diacetate and then into the glycol and the latter on oxidation with potassium permanganate was stated to give a dimethyl benzene dicarboxylic acid melting at 123°. No direct proof of the constitution of this acid was given; it was not even proved to be a phthalic acid. It had been shown previously, however, by SCHNAPAUFF [1]), that durene on oxidation gave two acids namely, 4 : 6 dimethyl *iso*phthalic acid melting above 320°, and 2 : 5 dimethyl terephthalic acid which did not melt. The constitutions of these two acids were definitely established and at the end of his paper SCHNAPAUFF states "Die dritte mögliche Dicarbonsäure, einer dimethylirte Orthophtalsäure, habe ich nicht beobachtet". It was no doubt for this reason that VON KORCZYNSKI assigned the above constitution to his acid. The whole scheme may be conveniently represented as follows:



The usual method of preparing phthalic acids is by the oxidation of benzene derivatives possessing ortho side chains but as SCHNAPAUFF'S experiments clearly indicate, this method cannot be applied in the case of durene. Further, since no other possible starting material for such an oxidation could be found, it was decided to use VON KORCZYNSKI'S method in the hope that it could be improved. Any other synthetic method seemed to be out of the question owing to the unusually great difficulties experienced in placing two carboxyl groups in ortho positions to each other by any method other than that just indicated.

(a) *The bromination of durene.*

The following method was found to give the largest yield of the required durylene dibromide.

Durene (10 grams), was heated in a small round flask fitted with a reflux condenser and a suitable delivery tube for hydrogen bromide, in a glycerol bath to 130° and the calculated quantity of bromine (24 grams), was passed into the molten hydrocarbon by means of a stream of dry carbon dioxide. The apparatus was placed in sunlight and the addition of bromine took 2—3 hours. The reaction took place

[1]) **Ber. 19,** 2509 (1886).

immediately and when all the bromine had been added, the product was distilled in a vacuum, when three principal fractions were obtained, namely,

(a)	—175°/13 mms.	(3 grams)
(b)	180°—200°/13 mms.	(7 grams)
(c)	above 200°/13 mms.	(7 grams)
(d)	undistillable	(3 grams)

The first fraction was an oil which on keeping deposited a small quantity of solid matter. This was separated and added to (b). The latter solidified completely on distillation and melted at 70°—120°. The third fraction was a thick oil which on keeping in the ice chest slowly crystallised to a pasty mass. Fraction (b) was crystallised from benzene or ethyl acetate and the durylene dibromide separated in long fine needles melting at 153°—156°. The mother liquors yielded a small quantity of the same substance, and after an elaborate recrystallisation a total yield of 2.2 grams of a substance melting at 155°—157° was obtained. The more soluble products from the mother liquors, when recrystallised from ethyl acetate, benzene or petroleum gave products of low melting point which were obviously mixtures and a fraction melting as low as 70°—80° was soon reached.

Unlike (b), fraction (c) was readily soluble in cold ethyl acetate, or benzene and also in ether, acetone and acetic acid. When attempts were made to crystallise it from petroleum in which it was most sparingly soluble, only oils which gradually became pasty were obtained.

Thus the only definite product which it was possible to isolate was a 10 per cent. yield of VON KORCZYNSKI'S dibromide and this only after a very tedious process.

The method of procedure was varied considerably but the above gave the best yield. It was also found that alcohol, although it was used by VON KORCZYNSKI, is not a suitable solvent for the recrystallisation of the above dibromide. Although the substance dissolved quite readily and crystallised quite well from this solvent, the solution was always red and if it was boiled for some time some of the dibromide reacted with the solvent and the yield was thereby diminished.

The higher boiling point products contained no appreciable quantity of mono or dibromodurene since on saponification with alkali and steam distillation no volatile bromo-compounds were obtained.

The conversion of durylene dibromide into dimethylbenzene dicarboxylic acid.

The durylene dibromide was converted into the corresponding durylene glycol in the usual manner by boiling it first with an alcoholic solution of anhydrous sodium acetate and then hydrolysing by means of caustic potash. The glycol was obtained as a waxy solid with an unsharp melting point in a yield of 80 per cent. Since it was not specially required it was not rigorously purified but oxidised directly as follows. The crude product was dissolved in a large quantity of

aqueous acetone in the cold and the solution cooled in ice and well stirred. The calculated quantity of potassium permanganate was then slowly added during five hours and after stirring for two hours longer the whole was left over night. Next day the alkaline liquid was filtered from the manganese oxide, the acetone distilled off and the residual solution again filtered. The clear filtrate was then acidified when a white crystalline precipitate, which gave the solution the appearance of starch paste, was formed. This was filtered off, washed and dried at 120°.

The crude acid thus obtained in very good yield had the following properties. When heated at 200° in a vacuum only the merest trace sublimed; in this respect it is totally different from 4 : 5 dimethylphthalic acid which was subsequently prepared in another way. On heating, it remained unchanged at 320° but melted and then immediately sublimed at 355°. On titration with standard alkali it gave an equivalent of 95.8 ($C_{10}H_{10}O_4$, requires 97). When heated with resorcinol and a drop of sulphuric acid it gave a fairly intense fluorescein reaction apparently showing that it contained some phthalic acid derivative. It was immediately obvious, however, that the acid described by VON KORCZYNSKI as melting at 123° had not been obtained.

The acid was very sparingly soluble in water even on boiling and it separated from the hot solution as a flocculent mass of microscopic needles. It was fairly easily soluble in hot alcohol from which it separated in very small transparent needles or long prisms. On heating the crystallised acid no definite melting point could be obtained; as a rule the acid gradually shrank and sublimed in the neighbourhood of 340°—350° but sometimes it was seen to melt at 355° and immediately sublime. When heated slowly over a free flame, however, it was clearly seen to melt suddenly and then sublime. The recrystallised acid still gave a fluorescein reaction with resorcinol although it was clearly not so intense as with the crude acid, nevertheless this reaction could not be eliminated altogether even after several recrystallisations. The acid after three recrystallisations gave the following analytical data,

0.1584 gram gave 0.0762 gram of H_2O and 0.3562 gram CO_2, H = 5.33 per cent.
C = 61.31 per cent. $C_{10}H_{10}O_4$ requires C = 61.85 per cent. H = 5.15 per cent.
0.1233 gram required 12.60 ccs. of 0.1 N. NaOH for neutralisation hence the equivalent is 97.8, $C_{10}H_{10}O_4$ requires 97.0.

These data clearly indicate that the acid consists for the most part of a dimethylbenzene dicarboxylic acid, it is true, but its properties are not those of a phthalic acid since it has an extremely high melting point and sublimes unchanged. It differed totally from 4 : 5 dimethyl phthalic acid prepared by other means and its crystalline form, solubility and behaviour on heating agree so well with the acid described by SCHNAPAUFF as 4 : 6 dimethyl isophthalic acid that there seemed to be no doubt about their identity. The only fact at variance with this conclusion is the fact that the acid definitely gave a positive fluorescein reaction which is characteristic of ortho dicarboxylic

acids. This reaction is so sensitive, however, that it does not of necessity follow that the acid is essentially an ortho phthalic acid. Further, the oxidation of the durene derivative might perhaps proceed further than the dicarboxylic stage, to some extent and therefore the crude acid might probably contain a certain amount of the higher carboxylic acids, which are ortho phthalic acids and would certainly give a fluorescein reaction.

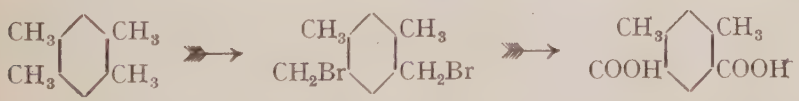
The analytical data cited above, make such an assumption appear highly improbable since the presence of any appreciable quanity of higher carboxylic acids would certainly show itself in the titration and combustion, and these impurities would be eliminated on recrystallisation.

It was subsequently discovered that the fluorescein reaction was caused by the oxidation of the methyl groups by the sulphuric acid, used as the condensing agent and it was also found that other benzene carboxylic acids containing ortho side chains, such as *o*-toluic acid, gave a more or less intense fluorescein reaction when heated with resorcinol and sulphuric acid. *When this acid was heated with resorcinol and anhydrous zinc chloride, however, no fluorescein reaction was obtained.* Thus on heating the four acids mentioned below, (a few milligrams) with half a gram of zinc chloride and a little resorcinol in the same air bath, maintained at 190°, for half an hour, the following results were obtained.

(a) phthalic acid — fluorescein reaction very strong
(b) *o*-toluic acid — nothing
(c) acid from durence above, the merest trace of fluorescence
(d) 4 : 5 dimethyl phthalic acid, an extremely intense reaction even stronger than in (a).

Thus these experiments prove beyond all doubt that *the acid obtained from durylene dibromide is not a dimethyl phthalic acid* as stated by VON KORCZYNSKI and since its properties agree exactly with those of the dimethyl isophthalic acid obtained directly by the oxidation of durene itself, it may be concluded that it has the same constitution.

It naturally follows from this conclusion that the durylene dibromide melting at 157°, is really 1 : 2 dimethyl 4 : 6 bromomethyl benzene and not 1 : 2 dimethyl 4 : 5 bromomethyl benzene as formally supposed ; the reactions here described being represented as follows:

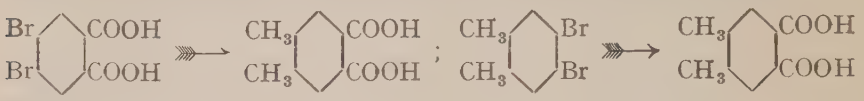


It should be stated here perhaps, that the above acid is obtained in excellent yield from the glycol and as far as could be ascertained it is the sole product of the reaction.

Thus it appeared that 4 : 5 dimethyl phthalic acid was unknown and therefore the following experiments were instituted in order to synthesise it.

(*b*) *The synthesis of* 4 : 5 *dimethyl phthalic acid.*

The first experiments were made with the view of replacing the bromine atoms in 4:5 dibromophthalic acid by methyl groups as:



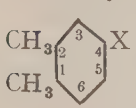
(A) (B)

The dibromoacid, the constitution of which has been determined by BRÜCK [1]), was prepared by brominating phthalic anhydride in 50 per cent. fuming sulphuric acid as described by JUVALATA [2]) and then converted into its dimethyl ester. The latter was crystallised from methyl alcohol before use and was obtained in long shining needles melting at 81°—82°. The ester was then boiled for 24 hours and longer with an excess of methyl iodide and sodium in absolute ether, a small quantity of ethyl acetate being added to facilitate the reaction but on working up the product 90 per cent. of the original ester was recovered unchanged. The experiment was varied by using benzene as the solvent but with no better success. The only product obtained besides unchanged ester was a very small amount of dark coloured oil which contained bromine and from which nothing definite could be isolated.

A second method represented by scheme (B) and depending on the GRIGNARD synthesis with magnesium and carbon dioxide, met with no better success.

A perusal of the literature for possible starting materials for the preparation of this acid, showed very clearly that the only available substances were 4-substituted *o*-xylenes and of these the most promising material appeared to be paraxylic acid, 3 : 4 dimethyl benzoic acid. The only thing required to convert this acid into the phthalic acid is the introduction of another carboxyl group in position 5, that is in the ortho position to the carboxyl group already present.

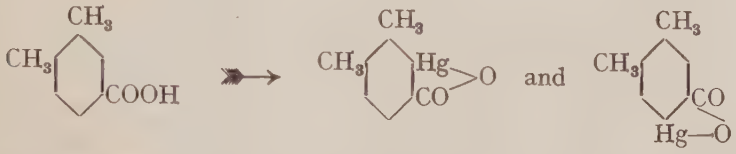
A study of the 4-substituted *o*-xylenes, which may be represented by the annexed formula and where X is either a carboxyl group or a grouping which could probably be converted into a carboxyl group, showed that in every case *the group* X *possessed a very strong directing influence to the meta position*, 6. This, with the ortho directing influence of the methyl group 1, made it highly probable that any fourth substituent in these compounds would enter the position 6 and not the position 5 as was required.



Use has been made however of the "abnormal" substitution of mercury in the benzene nucleus. It has been shown by PESCI [3]) and also by DIMROTH [4]) that when benzoic acid is fused with mercuric

[1]) Ber. **34**, 2741 (1901).
[2]) D. R-P. 50177; FRIEDLÄNDER II, 94.
[3]) Atti accad. Lincei (5) **9**, i, 255.
[4]) Ber. **35**, 2871 (1902).

acetate or anhydrous mercuric benzoate is heated for a sufficiently long time at 170°, the internal anhydride of *o*-hydroxymercuribenzoic acid is produced. The mercury atom thus introduced into the nucleus is very readily displaceable by other atoms or groups. Thus DIMROTH and SCHMAEDEL [1]) showed that it could be displaced by bromine or the sulphonic group yielding *o*-bromo-and *o*-sulpho-benzoic acids. This reaction has now been applied to paraxylic acid with similar results. In this case, however, the reaction is not so straight forward since there are two differently situated ortho positions to the carboxyl group and on that account two compounds, namely, 1 : hydroxymercuri- and 6 : hydroxymercuri- 2 : 3 dimethyl benzoic acids are produced in the mercuriation process, as :



The insolubility of these mercuric derivatives made it impossible to separate them but the two sulphonic acids derived from them were separable by the fractional crystallisation of their salts. The sulphonic group was then replaced by a carboxyl group by fusing the alkali salts with sodium formate.

Paraxylic acid, the starting material for this synthesis, was first prepared by FITTIG and LAUBINGER [2]) and later by PERKIN and BENTLEY [3]) by the oxidation of *ψ*-cumene with nitric acid. This method gives a mixture of paraxylic, xylic, methylisophthalic and methylterephthalic acids, the separation of which is rather laborious. More recently, however, LIEBERMANN and RAHTS [4]) obtained an almost theoretical yield of this acid by allowing a very large excess of oxalyl chloride to react with *o*-xylene in the presence of aluminium chloride according to the method given by LIEBERMANN and ZSUFFA [5]). This method for introducing carboxyl groups directly into the benzene nucleus by the FRIEDEL-CRAFT synthesis appears to be quite general but has only been carried out on small quantities in the presence of a very large excess of oxalyl chloride. The reaction depends on the intermediate formation of carbonyl chloride formed by the catalytic decomposition of the oxalyl chloride in the presence of aluminium chloride. The carbonyl chloride then reacts with the hydrocarbon giving the acid chloride but STAUDINGER [6]) has shown that the reaction may then go a stage further giving benzophenone or its derivatives. A study of the interaction of oxalyl chloride and *o*-xylene has shown

[1]) Ber. **40**, 2414 (1907).
[2]) Ann. **151**, 275 (1869).
[3]) J. Chem. Soc. **71**, 166 (1897).
[4]) Ber. **45**, 1204 (1912).
[5]) Ibid. **44**, 208 (1911).
[6]) Ibid. **41**, 3566 (1908).

that the reaction proceeds in two ways giving paraxylic acid and 4 : 4′ *o*-xylil, the latter being formed by the condensation of two molecules of *o*-xylene and one of oxalyl chloride as follows:

The corresponding ketone, 3 : 4 : 3′ : 4′ tetramethylbenzophenone, which was expected as a possible by-product, if formed at all, was only present in the reaction mixture in very small amount. It has already been prepared by BISTRZYCKI and REINTKE [1]) and could have been easily identified.

The synthesis of 4 : 4′ *o*-xylil in this manner, would appear to be the first synthesis of a benzil from a benzenoid hydrocarbon by the FRIEDEL-CRAFT method although STAUDINGER and SCHÖLLER [2]) and STAUDINGER, SCHLENKER and GOLDSTEIN [3]) obtained anisil from anisole and substituted naphthils from the naphthol ethers respectively and LIEBERMANN [4]) obtained a similar compound from anthracene.

The action of oxalyl chloride on o-xylene.

The most economical method of preparing paraxylic acid was as follows. Oxalyl chloride (45 grams), *o*-xylene (30 grams) and dry carbon disulphide (200 ccs.) were placed in a three necked round bottom flask, (500 ccs.), fitted with a very efficient stirrer with a mercury seal and a reflux condenser. The flask was then cooled in ice, the mixture well stirred and powdered aluminium chloride (50 grams) gradually added in very small quantities every five minutes during five hours. The mixture was usually stirred for one hour more and left over night. Next day a dark brown semi-solid product had separated; the stirring was recommenced and sufficient dilute hydrochloric acid added to dissolve all solid matter. The carbon disulphide was then distilled off on the water bath and the residue, which consisted of the aqueous solution and a dark brown oil, distilled in steam. A very small quantity of paraxylic acid passed over at first. This was due to the volatility of the chloride which is formed in the above reaction. The chloride is rapidly hydrolised however during the steam distillation and in about 10 minutes nothing more passed over and the brown oily reaction product was changed into a hard brown, granular solid. The latter was filtered when cool, well washed and boiled with sodium carbonate solution and again filtered. The residue, about 6 grams is the crude xylil.

The sodium carbonate solution was boiled with a little decolourising charcoal and the almost colourless solution on acidification with hydro-

) Ber. **38,** 844 (1905).
[2]) ibid. **45,** 1594 (1912).
[3]) Helvetica Chim. Acta **4,** 334 (1921).
[4]) Ber. **44,** 202, 852 (1911).

chloric acid gave almost pure paraxylic acid (35 grams). This was obtained quite pure in fairly large crystals melting at 166.5° (corr.), when once crystallised from strong acetic acid. The melting point usually given in the literature is 163°. In one experiment the paraxylic acid was extracted with caustic soda and it was discovered that the alkaline solution was strongly fluorescent. On crystallising the paraxylic acid from this solution the acetic acid was also strongly fluorescent but on cooling a small quantity of tarry matter first separated, the fluorescence disappeared and pure paraxylic acid separated later. Is is better to use sodium carbonate solution, however, since in this case the colouring matter is not extracted.

The above experiment was varied by using different amounts of oxalyl chloride. It was found that with increasing amounts the yield of paraxylic acid on the *o*-xylene used was only slightly increased, some by-product always being formed. When the amount used was diminished, however, the relative quantity of xylil rapidly increased, thus with equal quantities of *o*-xylene and oxalyl chloride the yield of acid was only 50 per cent. as against 75-80 per cent. in the above experiment.

4 : 4′ o-xylil and its derivatives.

The brown solid insoluble in sodium carbonate solution consists of 4 : 4 *o*-xylil together with some tarry matter. The xylil may be isolated as follows. The crude product is first distilled in a high vacuum. In this way most of the colouring matter is eliminated and a yellow solid melting at 105°—120° is obtained. The pure compound is obtained by recrystallisation from a large quantity of glacial acetic acid. It separates from this solvent in large citron yellow leaves which tend to retain the solvent to a slight extent. This is easily removed, however, by boiling the crystals with alcohol in which they are only sparingly soluble.

4 : 4′ *o*-xylil or 3 : 4 : 3′ : 4′ tetramethylbenzil is a citron yellow solid, melting at 128.5° (corr.), readily soluble in hot acetic acid or benzene but only sparingly soluble in ether and alcohol. The analysis gave

0.1690 gram gave 0.1038 gram of H_2O and 0.4982 gram of CO_2
C = 80.40 per cent. H = 6.82 per cent., $C_{16}H_{18}O_2$ requires C = 81.20 H = 6.76

Its constitution as a 1 : 2 diketone was established by the production of the following derivatives.

4 : 4′ o-xylil osazone.

The diketone (1 gram) was dissolved in hot glacial acetic acid and phenylhydrazine (2 grams) added. On heating the solution on the water bath for an hour and a half the osazone crystallised while still hot as a golden yellow, crystalline powder, sparingly soluble in all the commoner solvents which were tried.

4 : 4′ *o*-xylil osazone is a golden yellow crystalline solid, melting at

199° —200° (corr.). Its crystalline form as seen under the microscope is very characteristic, the crystals forming transparent six sided tablets which are rather longer than their breadth. On analysis:

0.1748 gram gave 18.0 ccs. of N at 15° and 763.8 mms., N = 12.08 per cent.
$C_{30}H_{30}N_4$, requires N = 12.55 per cent.

2 : 3- *di*(3 : 4-*dimethylphenyl*) *quinoxaline.*

This derivative was prepared in nearly quantitative yield by dissolving 2 grams of the diketone in 70 per cent. acetic acid, adding 5 grams of *o*-phenylene diamine hydrochloride and sodium acetate and heating for a couple of hours on the water bath. The diamine hydrochloride and sodium acetate readily dissolved and a colourless crystalline precipitate made its appearance. The latter was redissolved by bringing the solution to the boiling point and allowed to cool.

2 : 3- di(3 : 4-dimethylphenyl) quinoxaline crystallised in colourless needles melting at 158° (corr.). On analysis:

0.1616 gram gave 11.9 ccs. of N at 16° and 762.0 mms., N = 8.58 per cent.
$C_{24}H_{22}N_2$, requires N = 8.28 per cent.

This quinoxaline derivative could not be obtained by boiling a solution of the xylil with *o*-phenylene diamine in alcohol. On cooling the solution after boiling for one and a half hours, only slightly impure diketone separated.

The constitution of this xylil has not been definitely proved but since the first substituent in *o*-xylene invariably enters the 4 position, experiments to prove the orientation of the carbonyl groups were considered unnecessary.

The mercuration of paraxylic acid.

This was carried out by the two methods generally used for the introduction of the hydroxymercuri-group into benzoic acid.

Mercuric paraxylate has not been previously described but it is readily obtainable in the anhydrous condition by adding a slight excess of mercuric acetate solution to a cold solution of sodium paraxylate. The same compound is obtained in a more flocculent form from hot solutions. The fact that it was an ordinary salt was proved by its reactions with acids, alkalies and hydrogen sulphide.

The action of heat on mercuric paraxylate. (DIMROTH's method).

DIMROTH [1]) discovered that when anhydrous mercuric benzoate is heated at 170° benzoic acid sublimes and the internal anhydride of *o*-hydroxymercuri-benzoic acid results.

When mercuric paraxylate is similarly heated to 180° for four hours, nothing apparently happens, there is no alteration in appearance, no

[1]) loc. cit.

sublimate and the product may be heated to a high temperature in the same way as the original mercuric salt without melting ; it decomposes in the neighbourhood of 400°. A change has taken place however and the reactions of the product proved it to be the paraxylate of *o*-hydroxymercuriparaxylic acid, the original mercuric salt undergoing an isomeric change as :

This only represents one of the two mercuri-compounds which are formed. The product of the reaction has the same composition as mercuric paraxylate but except for a very small quantity of metallic mercury, it dissolves completely in caustic soda solution. On saturating the alkaline solution with carbon dioxide, the mixed internal anhydrides of the *o*-hydroxymercuriparaxylic acids are precipitated quantitatively and on acidifying the filtrate half the original paraxylic acid is recovered. This method of mercuration has the disadvantage that half the paraxylic acid remains unchanged. For this reason the following method was used to prepare the anhydrides in quantity.

The direct mercuration of paraxylic acid. (PESCI's method).

PESCI [1]) obtained the anhydride of *o*-hydroxymercuri-benzoic acid by fusing benzoic acid with mercuric acetate. This method has been applied as follows.

Molecular quantities of paraxylic acid (30 grams) and mercuric acetate (65 grams) were ground together, introduced into a distillation flask and heated in an oil bath. During the first 20 minutes the temperature was raised to 130°, the mass then became partly liquid and acetic acid began to distil. The heating was continued for one and a half hours and the temperature gradually increased to 170°. During the two hours heating 24 grams of acetic acid distilled and this was increased to 26 grams, the theoretical amount, in another hour. The heating was then stopped and the white solid mass ground to a fine powder. The crude product was treated with cold dilute caustic soda solution, in which it was nearly completely soluble and the solution filtered from the very small quantity of grey matter. The pure mixed *o*-hydroxymercuri-paraxylic acid anhydrides were then precipitated by saturating the alkaline solution with carbon dioxide. The white amorphous powder was filtered off and air dried. The yield was 67 grams or 97 per cent.

The analysis of this product proved to be rather difficult and even after long heating in oxygen there always remained a noncombustible residue. The latter consisted of a very small quantity of mineral

[1]) loc. cit.

matter which the amorphous mercury compounds most tenaciously held and a certain amount of unburnt carbon. The result was that the carbon was always rather low but the hydrogen was quite good. Two typical results were:

0.8984 gram gave 0.1826 gram H_2O, 0.9516 gram CO_2 and 0.0090 gram residue
0.7090 ,, ,, 0.1438 ,, H_2O, 0.7540 ,, CO_2 ,, 0.0144 ,, ,,
for $C_9H_8O_2Hg$, C = 31.03 per cent. H = 2.30 per cent.
found C = 28.89 (29.19) H = 2.26 (2.28)
= 29.00 (29.65) = 2.23 (2.30)

The results given in brackets are corrected for ash.

Orientation of the Mercury compounds.

When the above product was treated in neutral, faintly alkaline or faintly acid solution with a solution of bromine dissolved in potassium bromide, the result was always the same. The mercury compound dissolved, carbon dioxide was evolved and the solution became turbid. From this reaction product neutral and acidic substances were isolated. The former consisted of a semi-solid mass from which a specimen of pure 4 : 5 dibromo-*o*-xylene was readily obtained by crystallisation from alcohol. The acidic product melted at 120°—170° and could not be resolved into its constituent bromoacids by crystallisation.

These experiments showed that treatment with bromine replaced the mercury group and also the carboxyl to some extent and although pure 4 : 5 dibromo-*o*-xylene was obtained it was obvious from the mixture of bromo-acids that the original mercury compound was a mixture. This was subsequently confirmed .

Sulphonation of the mixed o-hydroxymercuri-paraxylic acid anhydrides.

Dimroth and Schmaedel proved that when *o*-hydroxymercuri-benzoic acid was treated at the ordinary temperature with 18 per cent. oleum it yielded a small quantity of benzoic acid and a mixture of *o.m.* and *p*-sulphobenzoic acids in which the ratio of *o* to $m + p$ was 6 : 1.

In the first experiment the above mercury derivatives were treated with 7 per cent. oleum but it was then found that the product consisted of some unchanged material, paraxylic acid and sulphonic acids. The following method which completely converted the mercury compounds into the corresponding sulphonic acids without the simultaneous formation of paraxylic acid and therefore, presumably, of the 6-sulphonic acid which would be formed by direct sulphonation, was eventually used.

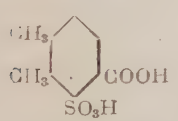
Into a round bottom flask, fitted with an adapter sloping upwards, were introduced 350 grams of 33 per cent. oleum which was cooled in ice and vigorously stirred. The finely divided mercury compounds, (66 grams), were then introduced into the adapter in very small quantities and the apparatus so arranged that as the heavy powder

fell from the end of the adapter it impinged on the rapidly revolving shaft of the stirrer. In this way the powder was dispersed in a cloud and fell uniformly into the oleum, any local rise in temperature being thereby avoided. The addition took place in two hours after which the liquid was stirred for two hours and then left overnight. Next day the semi-solid mass was poured into three litres of ice water when it dissolved completely to a pale brown solution, showing that there was no unchanged mercury compounds or paraxylic acid. The mercury was then removed as sulphide, the solution boiled with charcoal and the filtrate diluted to seven litres and treated with an excess of barium carbonate while still boiling. The filtrate contained the soluble barium salts of the sulphonic acids. These salts were not very soluble, hence the large volume of liquid used and further amounts were obtained on extracting the residual barium sulphate twice with boiling water. The total yield of barium salts was about 65 grams.

On evaporating the aqueous solution it was noticed that a sparingly soluble salt began to crystallise while the solution was still very dilute. When the solution had been reduced to approximately 100 ccs., about 40 grams had been deposited, yet the mother liquors yielded about 20 grams when evaporated to dryness. It was immediately obvious that there were two barium salts possessing very different solubilities. A more complete separation was effected by extraction as follows.

The barium salts were combined and extracted successively with 100 ccs. of water at 90° for an hour. The successive extracts on evaporation gave the following amounts of salt, 15.5, 10,2, 1.6, 1.5 and 1.3 grams. These were recombined and extracted which 200 ccs. of hot water and the 2.5 grams which remained undissolved added to the sparingly soluble portion. The filtrate on evaporation to dryness on a water bath gave 27 grams of the readily soluble barium salt as an almost white crystalline powder.

Subsequent experiments proved that this consisted of the monohydrated barium salt of 3-sulpho-paraxylic acid shown herewith. The analysis gave:



1.4508 gram lost 0.0721 gram on heating to 130° for one hour
0.4837 gram (anhydrous) gave 0.3086 gram of $BaSO_4$
Water = 4.97 per cent., Ba = 37.57 per cent.
$C_9H_8O_5SBa \cdot H_2O$, requires Water = 4.70, Ba (anhydrous) = 37.60

The sparingly soluble salt was dissolved in very much water and recrystallised. This salt apparently forms more than one hydrate. Thus on allowing the solution to cool and the salt to remain in contact with the mother liquors for a long time (2-5 days), the air dried salt is the tetrahydrate. By allowing a large proportion of the salt to crystallise while still hot and cooling, a product is obtained which contains very little water of crystallisation, (II), while if the salt is left in contact with the mother liquors for a short period say 15 hours, the amount of water of crystallisation has an intermediate value. The analyses were:

(I) 1.3212 grams lost 0.2101 gram, water = 15.91 per cent.
(II) 1.2642 „ „ 0.0440 „ „ 3.48 „ „
(III) 1.6876 „ „ 0.1758 „ „ 10.42 „ „
0.6250 gram (anhydrous) gave 0.3996 gram of $BaSO_4$. Ba = 37.64 per cent.
$C_9H_8O_5SBa$. 4 H_2O, requires water = 16.45 per cent. Ba = 37.60 per cent.

This salt proved to be the one required for the production of the dimethyl phthalic acid, namely the barium salt of the 5-sulpho-paraxylic acid.

The *sodium salts* of these sulphonic acids were prepared by boiling the corresponding barium salts with the calculated quantity of soda solution and crystallising from water. These salts did not show any marked difference in their solubilities, both were easily soluble in water.

Sodium 3-sulpho-paraxylate, from the soluble barium salt, crystallised from a very concentrated aqueous solution in a felted mass of silky needles which were difficult to filter. It was extremely soluble in hot water. Analysis of the air dried salt showed it to be a trihydrate.

1.6269 grams lost 0.2470 gram water = 15.25 per cent.
0.2746 gram (anhydrous) gave 0.1450 gram Na_2SO_4 Na = 17.0 per cent.

Sodium 5-sulpho-paraxylate was also quite easily soluble in water but unlike the compound just described it crystallised on cooling in very small, hard, brilliant crystals, which, when viewed under the microscope were found to consist of beautifully formed octagonal or square tablets. It might be mentioned here that the 4 : 5 derivatives of *o*-xylene invariably crystallise far more readily than the corresponding 3 : 4 derivatives. This is no doubt due to the molecular symmetry of these compounds. This sodium salt crystallises with two molecules of water. On analysis :

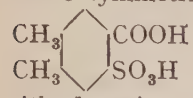
1.2693 grams lost 0.1431 gram on heating to 130° Water = 11.27 per cent.
0.2561 gram gave 0.1333 gram of Na_2SO_4 Na = 16.36 per cent. (anhydr.)
$C_9H_8O_5SNa_2 2H_2O$ requires Water = 11.61, Na = 16.78 per cent.

Orientation of the sodium sulpho-paraxylates.

The ortho orientation of the two acidic groupings was demonstrated by the fact that both these salts gave strongly fluorescent sulphonephthalein derivatives when warmed with resorcinol and a suitable condensing agent. The actual positions of these groups were determined by treatment with bromine. The sodium salt was dissolved in water and an excess of bromine dissolved in potassium bromide solution added and the mixture heated on the water bath for about one hour. The solution gradually became turbid and carbon dioxide was steadily evolved. After the reaction was complete the solution was made alkaline with sodium hydroxyde and the neutral dibromo-*o*-xylenes extracted with ether.

The sodium salt from the sparingly soluble barium salt gave about one third of its weight of a solid melting at 76°—80° but the melting point was raised to 85° when the solid was pressed. Crystallisation from alcohol raised the melting point still higher and the product was shown to

be 4 : 5 dibromo-*o*-xylene by direct comparison with a sample prepared by CROSSLEY's method from *o*-xylene [1]). This salt must be that of the symmetrical sulphonic acid shown here.



The other salt to be an ortho compound must be the 3-sulphonic acid as already stated and this is confirmed by the fact that on similar treatment with bromine an oily, fairly mobile *o*-xylene dibromide is obtained which shows no sign of crystallisation at ordinary temperatures. This is in complete agreement with the properties of 3 : 4 dibromo-*o*-xylene [2]).

The alkaline solutions from these dibromo-compounds gave a bromo acid on acidification. These acids and various other monosubstituted paraxylic acids will form the subject of a subsequent communication.

Preparation of 4 : 5 *dimethyl phthalic acid.*

V. MEYER [3]) demonstrated that the sulphonic group could not be replaced by the nitrile group by the usual method if a carboxyl group was also present in the molecule. A new method was therefore required and this he discovered by fusing the alkali salts of the sulphobenzoic acid with sodium formate. In this manner he obtained isophthalic acid in 18 per cent. yield when the experiment was successful.

This method has been applied to the 5-sulpho-paraxylate described above and dimethyl phthalic acid has been obtained in very small quantity. Many experiments have been carried out but the following procedure gave by far the best result.

Equal weights of the dehydrated sodium sulphonate and sodium formate (usually about 5 grams) were intimately mixed and heated in a nickel crucible over a free flame. At about 300° the solid showed signs of melting but it was not liquid till the temperature had reached 350°. From this temparature to 360° the whole mass became fluid and hydrogen was evolved. The temperature was carefully kept at this temperature for one and a half hours and the melt constantly stirred. The latter became very black and gradually resolidified. After the heating, the product, which was alkaline, was dissolved in water and filtered. The filtrate was then heated to boiling, acidified with hydrochloric acid and filtered hot. On cooling the pale brown solution deposited the crude acid. The latter which weighed about 0.6 gram was extracted with ether and purified as follows.

The acid was first sublimed and it was immediately shown to be a mixture, since the sublimate clearly consisted of two kinds of crystals. These sublimations were conveniently carried out in an apparatus consisting of a boiling tube down the centre of which passed a tube of about two thirds its diameter and which was well cooled by a current of cold water circulating through it. The two tubes were ground together at the mouth of the wider one and the annular space was

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[1]) J. Chem. Soc. **103**, 990 (1913).
[2]) O. JACOBSEN, Ber. **17**, 2377 (1884).
[3]) Ann. **156**, 272 (1870).

evacuated. The crude acid was placed in the bottom of the outer tube, the apparatus evacuated and then heated in a bath to about 200°. Practically the whole of the crude acid sublimed and collected on the end of the cool tube, which was then removed carefully and the sublimate taken away. No sublimate was found anywhere else but on this tube. The removal was thus complete and there was absolutely no loss. After the first sublimation which served to remove a small amount of charred matter, the product was resublimed and collected in three approximately equal fractions, which melted at 143°—160°, 150°—160°, and 205°—206° respectively.

The last fraction consisted of almost pure dimethyl phthalic anhydride. A further quantity of the latter was obtained by heating the impure fractions at 200° for a few minutes, dissolving in ether and shaking the solution with sodium bicarbonate solution to free it from acids. The ethereal solution on evaporation gave the anhydride. On acidification the sodium bicarbonate solution gave a product, consisting principally of paraxylic acid.

The anhydride was again treated with sodium bicarbonate and crystallised from ether.

4 : 5 *dimethyl phthalic anhydride* thus obtained, crystallises in characteristic square leaves melting at 208.5° (corr.). Its constitution as the anhydride of a dibasic acid was clearly proved by its behaviour towards alkalies. Thus it was soluble in sodium carbonate solution only on long boiling and on back titrating the solution using methyl orange as indicator the substance had an equivalent of 172. This was the mean of three experiments, which varied by ten per cent., a better agreement being impossible owing to the unsharp end point. The anhydride was much more easily soluble in caustic soda. In this case, using phenolphthalein as the indicator the equivalent was 90. ($C_{10}H_8O_3$ requires 88 as a dibasic anhydride). These two results clearly show the dibasicity of the acid.

4 : 5 *dimethyl phthalic acid* was obtained from the above anhydride by dissolving it in caustic soda and adding acid. It was obtained in colourless needles sometimes several centimeters in length, on crystallisation from water. When heated rapidly it showed some signs of melting in the neighbourhood of 200° then at 209° it melted with violent frothing due to the disengagement of water vapour. After the disengagement of water vapour had ceased the resulting anhydride melted sharply at 208°—208.5°. On titration:

0.2028 gram required 14.41 ccs. of 0.1445 n. NaOH, Equivalent = 97.4
$C_{10}H_{10}O_4$, requires 97.1.

The silver salt was obtained as an insoluble white solid in the usual manner. On analysis:

0.1255 gram gave 0.0662 gram of silver. Ag = 52.76 per cent.
$C_{10}H_8O_4Ag_2$ requires Ag = 52.93 per cent.

Attempts to reduce this acid to the corresponding hexahydro-derivative have not yet been successful but experiments are in progress with this point in view.

Summary.

(1.) The previous work on cantharidin especially after 1913, is reviewed and from it, it is concluded that the formula accepted by RUDOLF and later by GADAMER rests on insufficient experimental evidence. In view of the extensive researches of GADAMER and his collaborators on cantharidin itself, it appears to be very difficult to institute further investigations of an analytical nature, which would lead to conclusive evidence that would definitely settle the constitution. It was therefore decided to prepare compounds having the three structures originally suggested for deoxycantharidin by GADAMER synthetically, since by this means it should be possible to determine the constitution of the product from the natural source.

(2). The interaction between ethyl sodiomalonate and dibromo*cyclo*hexene has been studied and has been found to take place in two directions leading to *cyclo*hexene and ethyl ethanetetracarboxylate on the one hand and hexahydro-*iso*coumaranone on the other.

(3). Ethyl ethanetetracarboxylate reacts towards hydrazine as a normal ester.

(4). The interaction of ethyl sodiomalonate and *cyclo*hexene halogenohydrins has been studied.

(5). The best method of preparing hexahydro-*iso*coumaranone is by the interaction of ethyl sodiomalonate and *cyclo*hexene oxide.

(6). Several derivatives of *cyclo*hexanol malonic and acetic acids have been described.

(7). 1 : 2 *cyclo*hexane diacetic acid could not be obtained from hexahydro*iso*coumarone.

(8). Various attempts have been made discover a more suitable method for preparing *o*-phenylene diacetic acid but the method described by MOORE and THORPE has been found to be the most suitable.

(9). In this connection dihydronaphthalene has been ozonised; a very stable mono-ozonide is obtained which was decomposed with water only with the greatest difficulty.

(10.) Ortho-phenylene diacetic acid is left unaffected by treatment with sodium and ethyl or amyl alcohol but it is quantitatively reduced to a mixture of *cis-* and *trans- cyclo*hexane diacetic acids with the help of platinum black and hydrogen.

(11). The separation of these two acids proved to be a very difficult matter but the *cis-* acid has been obtained pure and it has been definitely proved that it is not identical with deoxycantharidinic acid. *It may be definitely concluded therefore that cantharidin is not a derivative of this particular acid as has been suggested.*

(12). VON KORCZYNSKI claimed to have prepared 4 : 5 dimethyl phthalic acid from durene. His work has been repeated and found to be incorrect.

(13). Durene on bromination at 130° in sunlight gives a complex mixture of products from which it is possible to isolate a ten per cent. yield of 2 : 4 dibromomethyl 1 : 5 dimethylbenzene, which was sup-

posed to be the 4 : 5 dibromomethyl compound by VON KORCZYNSKI. This compound on hydrolysis and oxidation gives the corresponding dimethyl isophthalic acid and not the orthophthalic acid as was supposed.

(14). Isophthalic acids with ortho side chains to the carboxyl groups, when heated with resorcinol and sulphuric acid give the fluorescein test owing to the oxidation of these side chains to carboxyl groups. When zinc chloride is the condensing agent, however, these acids do not give the fluorescein test.

(15). Attempts to prepare 4 : 5 dimethyl phthalic acid from 4 : 5 dibromo-*o*-xylene or 4 : 5 dibromophthalic acid were unsuccessful.

(16). The action of oxalyl chloride on *o*-xylene in the presence of aluminium chloride has been studied. The reaction takes place in two directions paraxyloyl chloride and 4—4′ *o*-xylil, some derivatives of which are described, being produced.

(17). Paraxylic acid is easily mercurated either by heating paraxylic acid with mercuric acetate or by heating mercuric paraxylate, giving a mixture of the anhydrides of the two possible *o*-hydroxymercuriparaxylic acids.

(18). The mixed hydroxymercuri compounds are easily converted into the corresponding *o*-sulpho-paraxylic acids which are obtained pure by the fractional crystallisation of the barium and sodium salts.

(19). These sulpho-paraxylic acids were orientated by treatment with an aqueous solution of bromine ; in each case carbon dioxide and the sulphonic groups are eliminated with the production of known dibromo-*o*-xylenes.

(20). 4 : 5 dimethyl phthalic acid has now been prepared by fusing the sodium salt of 5-sulpho-paraxylic acid with sodium formate.

STELLINGEN

I.

De verklaring van TRAUBE en LEHMANN voor de inwerking van natrium-aethyl-malonester op alkyleen-oxyden is niet juist.

Ber. **32,** 720 (1899); **34,** 1971 (1901).

II.

VON KORCZYNSKI heeft 4 : 5 dimethylphtaalzuur niet in handen gehad

Ber. **35,** 871 (1902).

III.

Het verdient aanbeveling, om de fluoresceïne-reactie op ortho-dicarboonzuren in plaats van met zwavelzuur met zinkchloride als condensatiemiddel uit te voeren.

IV.

Het is waarschijnlijk, dat de werking van siccatieven bij de oxydatie van drogende oliën niet alleen een katalytische is.

J. Chem. Soc. **121**, 17 (1922).

V.

Fargher's verklaring voor de vorming van polyarseniden is onvoldoende.

J. Chem. Soc. **117,** 866 (1920).

VI.

Het is noodzakelijk, de opvatting van Claisen omtrent de synthese van acetylazijnester te herzien.

Scheibler en Ziegner, Ber. **55,** 789 (1922).

VII.

Betaïnen hebben geen ringstructuur.

Pfeiffer, Ber. **55,** 1762, 1769 (1922).

VIII.

Het is beter, het *l*-glucosan van Pictet *β*-glucosan te noemen.

J. Chem. Soc. **119,** 1744 (1921).

IX.

Metaalhydriden zijn ware analoga van de halogeenzouten.

Bijvoet en Karssen, Verslag Akad. Wetenschappen, Amsterdam, **31,** 49 (1922).

Bardwell, J. Am. Chem. Soc. **44,** 2499 (1922).

X.

Thiosulfaten zijn verbindingen met twee- en zeswaardige zwavel.

Lindh, Compt. rend. **175,** 25 (1922).

XI.

GOLODETS' reactie is niet specifiek voor benzoylperoxyde.

Rec. trav. chim. **41**, 224 (1922)

XII.

Het laatste atoommodel van BOHR is te verkiezen boven dat van LANGMUIR.

Z. Physik **9**, 1 (1922)

DRUKKERIJ A.W. SIJTHOFF - LEIDEN